BMJ Open

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

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2016-014726
Article Type:	Protocol
Date Submitted by the Author:	13-Oct-2016
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, J.; West China Hospital, Sichuan University, Department of Geriatrics 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
Keywords:	delirium, systematic review and meta-analysis, incidence, Cardiac surgery < SURGERY

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

Yulin Liao (first author)

Department of Geriatrics , West China Hospital, Sichuan University

No. 37, Guo Xue Xiang, Chengdu, Sichuan, CHINA

Joseph H. Flaherty, MD

Division of Geriatrics, Department of Internal Medicine, Saint Louis University

1402 S. Grand Blvd, Room M238, St. Louis, MO, 63104, USA

flaherty@slu.edu

Jirong Yue, MD (corresponding author)

Department of Geriatrics , West China Hospital, Sichuan University

No. 37, Guo Xue Xiang, Chengdu, Sichuan, CHINA

Email:yuejirong11@hotmail.com; Tel : +8618980601143

Yanyan Wang

Department of Geriatrics , West China Hospital, Sichuan University

No. 37, Guo Xue Xiang, Chengdu, Sichuan, CHINA

Chuanyao Deng

Department of Geriatrics , West China Hospital, Sichuan University

No. 37, Guo Xue Xiang, Chengdu, Sichuan, CHINA

Ling Chen

Department of Geriatrics , West China Hospital, Sichuan University

No. 37, Guo Xue Xiang, Chengdu, Sichuan, CHINA

The authors have no commercial or financial conflicts to disclose.

Word count: 1517

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 researchin this area.

Trial registration number: CRD42016047773

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

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 researchin 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

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 orthopaedic 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%)[6-9] 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.[10]

Lastly, the incidence of postoperative delirium vary depending on characteristics of patients and types of surgery.[6-9] For example, delirium is more common among older patients with baseline cognitive impairment compared with patients with normal cognitive function.[11,12] Type of cardiac surgery is another factor that affects the incidence of delirium.[13,14]

A systematic review and meta-analysis that analyzes 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.

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 is available) that might have higher than average expected incidence. These characteristics include but are not limited to: age 80 years and older, baseline cognitive impairment, diabetes mellitus, depression and cerebrovascular disease, all of which have been found in a previous meta-analysis on risk factors associated with occurrence of delirium.[15]

METHODS

Criteria for included studies

We will conduct a comprehensive search on databases of MEDLINE, EMBASE, and The Cochrane Library from their inceptions through September 2016. 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".

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;studies that provide the data necessary to calculate incidence. We will exclude: (1) retrospective studies and interventional studies; (2) Studies that only report prevalence of delirium because it is not clear in these studies if patients had delirium pre-operatively. Incident delirium is preferred to investigate the actual situation of delirium after cardiac surgery.

Studies will be limited to human subjects aged 60 or over. The population of interest will be older hospitalized 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.

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

higher than the minimum sample size will be classified as "with good precision". Small-study effect on the effect size will be explored by the funnel plots, and asymmetry 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 % confidence intervals (CIs). We will derive SEs where studies have provided the corresponding numerator and denominator for delirium incidence estimates. Statistical heterogeneity across studies will be assessed by the Cochrane Q test and quantified by calculating the I^2. A value of I^2 greater than 50% indicates substantial heterogeneity. Where heterogeneity is statistically significant, we will conduct a sub-group analysis to investigate the possible sources of heterogeneity according the following variables: age, types of surgery, methods used for delirium diagnosis or assessment, pre-existing cognitive impairment diabetes mellitus, depression and cerebrovascular disease[15]. Furthermore, a sensitivity analysis will be performed to find out how our results would change if only high-quality studies were considered. Data will be analyzed by using Stata13.1 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), and of meta-analyses of observational studies (MOOSE).

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.

Funding

This research received no specific grant from any funding agency in the public, commercial or not-for-profit sectors.

REFERENCES

1. Saczynski JS, Marcantonio ER, Quach L, et al. Cognitive trajectories after postoperative delirium. *N Engl J Med*. 2012;367(1):30-9.
2. Joost Witlox M, Lisa S. M. Eurelings M, Jos F. M. de Jonghe P, et al. Delirium in Elderly Patients and the Risk of Postdischarge Mortality, Institutionalization, and Dementia: A Meta-analysis. *JAMA*. 2010;304(4):443-51.
3. Shi Q, Presutti R, Selchen D, Saposnik G. Delirium in acute stroke: A systematic review and meta-analysis. *Stroke*. 2012;43(3):645-649.
4. Barron EA, Holmes J. Delirium within the emergency care setting, occurrence and detection: a systematic review. *Emerg Med J*. 2013;30:263–268..
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(2):197-214.
6. Elizabeth L, Whitlock B, Andrea Vannucci M, et al. Postoperative Delirium. *Minerva Anestesiol*. 2011;77(4):448-56.
7. Eiseman TNRB. Postoperative delirium in the elderly: diagnosis and management. *Clin Interv Aging*. 2008;3(2):351-5.
8. Inouye SK, Westendorp RGJ, Saczynski JS. Delirium in elderly people. *Lancet*. 2014;383(9920):911-22.
9. Rudolph JL, Marcantonio ER. Review articles: postoperative delirium: acute change with long-term implications. *Anesth Analg*. 2011;112(5):1202-11.
10. Mu JL, Lee A, Joynt GM. Pharmacologic agents for the prevention and treatment of delirium in patients undergoing cardiac surgery: systematic review and metaanalysis. *Critic Care Med*. 2015;43(1):194-204.
11. Fong TG, Davis D, Growdon ME, et al. The interface between delirium and dementia in elderly adults. *Lancet Neurol*. 2015;14(8):823-32.
12. Jankowski CJ, Trenerry 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(5):1186-93.
13. Schenning KJ, Deiner SG. Postoperative Delirium in the Geriatric Patient. *Anesthesiol Clin*. 2015;33(3):505-516.
14. Vasilevskis EE, Han JH, Hughes CG, et al. Epidemiology and risk factors for delirium across hospital settings. *Best Pract Res Clin Anaesthesiol*. 2012;26(3):277-87.
15. 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.
16. 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(9):934-9.
17. Donna F. Stroup, Jesse A. Berlin, Sally C. Morton, et al. Meta-analysis of Observational Studies in Epidemiology : A Proposal for Reporting. *JAMA*. 2008;283(15):2008-1012.

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.**

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.

BMJ Open

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

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2016-014726.R1
Article Type:	Protocol
Date Submitted by the Author:	05-Jan-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

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

Yulin Liao (first author)

Department of Geriatrics, West China Hospital, Sichuan University

No. 37, Guo Xue Xiang, Chengdu, Sichuan, CHINA

Joseph H.Flaherty, MD

Division of Geriatrics, Department of Internal Medicine, Saint Louis University

1402 S. Grand Blvd, Room M238, St. Louis, MO, 63104, USA flaherty@slu.edu

Jirong Yue, MD (corresponding author)

Department of Geriatrics, West China Hospital, Sichuan University

The national center for Geriatric clinical research in West China Hospital

No. 37, Guo Xue Xiang, Chengdu, Sichuan, CHINA

Email: yuejirong11@hotmail.com; Tel: +8618980601143

Yanyan Wang

Department of Geriatrics, West China Hospital, Sichuan University

No. 37, Guo Xue Xiang, Chengdu, Sichuan, CHINA

Chuanyao Deng

Department of Geriatrics, West China Hospital, Sichuan University

No. 37, Guo Xue Xiang, Chengdu, Sichuan, CHINA

Ling Chen

Department of Geriatrics, West China Hospital, Sichuan University

No. 37, Guo Xue Xiang, Chengdu, Sichuan, CHINA

The authors have no commercial or financial conflicts to disclose.

Word count: 1648

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).

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

incidence of postoperative delirium varies depending on characteristics of patients and types of surgery.[6-9] For example, delirium is more common among older patients with baseline cognitive impairment compared with patients with normal cognitive function.[13,14] Type of cardiac surgery is another factor that affects the incidence of delirium.[15,16] A systematic review and meta-analysis that analyzes 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 recognize for researchers who recruit participants into study protocols so that the researchers will measure all potential baseline variables that increase risk of postoperative delirium in both the interventions 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 is available) that might have higher than average expected incidence. These characteristics include but are not limited to: age 65 and older, (including two subgroups 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 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)

Retrospective studies and interventional studies. (2) Studies that only report prevalence of delirium because it is not clear in these studies if patients had delirium pre-operatively. Incident delirium is preferred to investigate the actual situation 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 clinician in the clinical work. Instruments such as the Confusion-Assessment Method (CAM)[19], Delirium-Rating Scale (DRS)[20], Delirium Symptom Interview (DRI)[21] and so forth have been proven validated against DSM or ICD criteria. Studies using any method above for delirium diagnosis are acceptable in our review. Studies using non-validated instruments, such as Mini-mental-Status Exam (MMSE) [22]and Short Mental-Status Test (SMST)[23] will be excluded, for the reason that they are developed to measure cognitive impairment rather than delirium.[24]

Studies will be limited to human subjects aged 60 or over. The population of interest will be older hospitalized 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 by using a flow process chart.

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 and the Cochrane guidelines.[25,26] 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 higher than the minimum sample size will be classified as "with good precision." Small-study effect on the effect size will be explored by the 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 % confidence intervals (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 by using a random effects, after stabilizing the variance of individual studies with the Freeman-Tukey double arc-sine transformation.[27] Statistical heterogeneity across studies will be assessed by the Cochrane Q test and quantified by calculating the I^2. A value of I^2 greater than 50% indicates substantial heterogeneity. Where heterogeneity is statistically significant, we will conduct a sub-group analysis to investigate the possible sources of heterogeneity according the following variables: age, types of surgery, methods used for delirium diagnosis or assessment, pre-existing cognitive impairment diabetes mellitus, depression and cerebrovascular disease.[17] As different diagnostic methods for delirium have various sensitivity and specificity[28]

and this may influence the incidence of delirium to some extent[29], we will also perform subgroup analysis 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 funnel plot will be used to assess the publication bias across studies or selective reporting bias. Data will be analyzed by using Stata13.1 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)[30], and of meta-analyses of observational studies (MOOSE).[26]

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.

A major possible limitation of this study may be the heterogeneity of studies, since 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.

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

authors approved the final version.

Competing interests

None.

Funding

This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

REFERENCES

1. SaczynskiJS, Marcantonio ER, Quach L, et al. Cognitive trajectories after postoperative delirium. N Engl J Med. 2012;367(1):30-9.
2. JoostWitlox M, Lisa S. M. Eurelings M, Jos F. M. de Jonghe P, et al. Delirium in Elderly Patients and the Risk of Postdischarge Mortality, Institutionalization, and Dementia: A Meta-analysis. *JAMA*. 2010;304(4):443-51.
3. Shi Q, Presutti R, Selchen D, Saposnik G. Delirium in acute stroke: A systematic review and meta-analysis. Stroke. 2012;43(3):645-649.
4. Barron EA, Holmes J. Delirium within the emergency care setting, occurrence and detection: a systematic review. Emerg Med J. 2013;30:263–268.
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(2):197-214.
6. Elizabeth L, Whitlock B, Andrea Vannucci M, et al. Postoperative Delirium. Minerva Anestesiol. 2011;77(4):448-56.
7. Eiseman TNRB. Postoperative delirium in the elderly: diagnosis and management. Clin Interv Aging. 2008;3(2):351-5.
8. Inouye SK, Westendorp RGJ, Saczynski JS. Delirium in elderly people. Lancet. 2014;383(9920):911-22.
9. Rudolph JL, Marcantonio ER. Review articles: postoperative delirium: acute change with long-term implications. Anesth Analg. 2011;112(5):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 CardiovascNurs. 2013;12(3):284-292.
11. Norkiene I, Ringaitiene D, Kuzminskaite 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. Critic Care Med. 2015;43(1):194-204.
13. Fong TG, Davis D, Growdon ME, et al. The interface between delirium and dementia in elderly adults. Lancet Neurol. 2015;14(8):823-32.
14. Jankowski CJ, Trenerry 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(5):1186-93.

15. Schenning KJ, Deiner SG. Postoperative Delirium in the Geriatric Patient. Anesthesiol Clin. 2015;33(3):505-516.

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(3):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(6):1677-1687.

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(12): 941–948.

20. Trzepacz PT, Baker RW, Greenhouse J. A symptom rating scale for delirium. *Psychiat Res;* 1998; 23(1): 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(1): 14–21.

22. 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 (3): 189-198.

23. Kokmen E, Naessens JM, Offord KP. A short test of mental status: Description and preliminary results. *Mayo Clin Proc.* 1987; 62 (4): 281-288.

24. Smith MJ, Breitbart WS, Platt MM. A critique of instruments and methods to detect, diagnose, and rate delirium. *J Pain Symptom Manag.* 1995; 10 (1): 35-77.

25. 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(9): 934-9.

26. Donna F, Stroup P, MSc,et al. Berlin S, Sally C. Morton P, Ingram Olkin P, G. David Williamson P, Drummond Rennie M, et al. Meta-analysis of Observational Studies in Epidemiology : A Proposal for Reporting. *JAMA.* 2008;283(15): 2008-1012.

27. BarendregtJJ, Doi SA, Lee YY, et al. Meta-analysis of prevalence. *J Epidemiol Community Health*. 2013;67(11): 974-978.

28. Wong CL, Holroyd-Leduc J, Simel DL, Straus SE. Does this patient have delirium?: value of bedside instruments. *JAMA*. 2010; 304(7):779-786.

29. Laurila JV, Pitkala KH, Strandberg TE, Tilvis RS. The impact of different diagnostic criteria on prevalence rates for delirium. *Dement Geriatr Cogn*. 2003; 16 (3): 156-162.

30. 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.

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

43、6 and 32 and 42

EMBASE (OVID)

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

BMJ Open

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

Journal:	*BMJ Open*
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

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

Yulin Liao (first author)

Department of Geriatrics, West China Hospital, Sichuan University

No. 37, Guo Xue Xiang, Chengdu, Sichuan, CHINA

Joseph H.Flaherty, MD

Division of Geriatrics, Department of Internal Medicine, Saint Louis University

1402 S. Grand Blvd, Room M238, St. Louis, MO, 63104, USA flaherty@slu.edu

Jirong Yue, MD (corresponding author)

Department of Geriatrics, West China Hospital, Sichuan University

The national center for Geriatric clinical research in West China Hospital

No. 37, Guo Xue Xiang, Chengdu, Sichuan, CHINA

Email: yuejirong11@hotmail.com; Tel: +8618980601143

Yanyan Wang

Department of Geriatrics, West China Hospital, Sichuan University

No. 37, Guo Xue Xiang, Chengdu, Sichuan, CHINA

Chuanyao Deng

Department of Geriatrics, West China Hospital, Sichuan University

No. 37, Guo Xue Xiang, Chengdu, Sichuan, CHINA

Ling Chen

Department of Geriatrics, West China Hospital, Sichuan University

No. 37, Guo Xue Xiang, Chengdu, Sichuan, CHINA

The authors have no commercial or financial conflicts to disclose.

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).

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. The findings of this study will be presented at conferences and disseminated through publication in a peer-reviewed journal.

Trial registration number: CRD42016047773

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

Strengths and Limitations of this study: (1) This study will provide an up to date and accurate incidence of postoperative delirium in the elderly after cardiac surgery. (2) A subgroup analysis of certain patient characteristics make it possible to determine the incidence for specific population and screen the populations with higher than average risk of delirium. (3) The findings of this study will help guide researchers as they develop intervention trials to prevent delirium in the older population. (4) Non-English articles will not be included in our study due to language difficulties and this may cause publication bias to some extent.

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

incidence of postoperative delirium varies depending on characteristics of patients and types of surgery.[6-9] For example, delirium is more common among older patients with baseline cognitive impairment compared with patients with normal cognitive function.[13,14] Type of cardiac surgery is another factor that affects the incidence of delirium.[15,16] A systematic review and meta-analysis that analyzes 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 recognize for researchers who recruit participants into study protocols so that the researchers will measure all potential baseline variables that increase risk of postoperative delirium in both the interventions 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 is available) that might have higher than average expected incidence. It has been confirmed that there are numerous risk factors or patient characteristics associated with delirium, but some of them are mentioned much more often and we will conduct subgroup-analysis based on these characteristics. These characteristics include but are not limited to: age 65 and older, (including two subgroups

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

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) Retrospective studies and interventional studies. (2) Studies that only report prevalence of delirium because it is not clear in these studies if patients had delirium pre-operatively. Incident delirium is preferred to investigate the actual situation 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 clinician in the clinical work. Instruments such as the Confusion-Assessment Method (CAM)[19], Delirium-Rating Scale (DRS)[20], Delirium Symptom Interview (DRI)[21], Intensive Care Delirium Screening Checklist (ICDSC)[22] and so forth have been proven validated against DSM or ICD criteria. Studies using any method above for delirium diagnosis are acceptable in our review. Studies using non-validated instruments, such as Mini-mental-Status Exam (MMSE) [23]and Short Mental-Status Test (SMST)[24] will be excluded, for the reason that they are developed to measure cognitive impairment rather than delirium.[25]

Studies will be limited to human subjects aged 60 or over. The population of interest will be older hospitalized 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 by using a flow process chart.

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 and the Cochrane guidelines.[26,27] 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 higher than the minimum sample size will be classified as "with good precision." Small-study effect on the effect size will be explored by the funnel plots, and a 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 % confidence intervals (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 by using a random effects, after stabilizing the variance of individual studies with the Freeman-Tukey double arc-sine transformation.[28] Statistical heterogeneity across studies will be assessed by the Cochrane Q test and quantified by calculating the I^2. A value of I^2 greater than 50% indicates substantial heterogeneity. Where heterogeneity is statistically significant, we will conduct a sub-group analysis to investigate the possible sources of heterogeneity

according the following variables: age, types of surgery, methods used for delirium diagnosis or assessment, pre-existing cognitive impairment diabetes mellitus, depression and cerebrovascular disease.[17] As different diagnostic methods for delirium have various sensitivity and specificity[29] and this may influence the incidence of delirium to some extent[30], we will also perform subgroup analysis 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 funnel plot will be used to assess the publication bias across studies or selective reporting bias. Data will be analyzed by using Stata 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)[31], and of meta-analyses of observational studies (MOOSE).[27]

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 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 intervention

trials to prevent this important syndrome in the older population. Furthermore, understanding baseline (preoperative) patient characteristics that increase postoperative delirium is critical for balanced randomization in intervention trials to prevent postoperative delirium.

A major possible limitation of this study may be the heterogeneity of studies, since 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.

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 authors approved the final version.

Competing interests

None.

Funding

This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

REFERENCES

1. SaczynskiJS, Marcantonio ER, Quach L, et al. Cognitive trajectories after postoperative delirium. N Engl J Med. 2012;367(1):30-9.
2. JoostWitlox M, Lisa S. M. Eurelings M, Jos F. M. de Jonghe P, et al. Delirium in Elderly Patients and the Risk of Postdischarge Mortality, Institutionalization, and Dementia: A Meta-analysis. *JAMA*. 2010;304(4):443-51.
3. Shi Q, Presutti R, Selchen D, Saposnik G. Delirium in acute stroke: A systematic review and meta-analysis. Stroke. 2012;43(3):645-649.
4. Barron EA, Holmes J. Delirium within the emergency care setting, occurrence and detection: a systematic review. Emerg Med J. 2013;30:263–268.
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(2):197-214.
6. Elizabeth L, Whitlock B, Andrea Vannucci M, et al. Postoperative Delirium. Minerva Anestesiol. 2011;77(4):448-56.
7. Eiseman TNRB. Postoperative delirium in the elderly: diagnosis and management. Clin Interv Aging. 2008;3(2):351-5.

8. Inouye SK, Westendorp RGJ, Saczynski JS. Delirium in elderly people. Lancet. 2014;383(9920):911-22.
9. Rudolph JL, Marcantonio ER. Review articles: postoperative delirium: acute change with long-term implications. Anesth Analg. 2011;112(5):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 CardiovascNurs. 2013;12(3):284-292.
11. Norkiene I, Ringaitiene D, Kuzminskaite 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. Critic Care Med. 2015;43(1):194-204.
13. Fong TG, Davis D, Growdon ME, et al. The interface between delirium and dementia in elderly adults. Lancet Neurol. 2015;14(8):823-32.
14. Jankowski CJ, Trenerry 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(5):1186-93.
15. Schenning KJ, Deiner SG. Postoperative Delirium in the Geriatric Patient. Anesthesiol Clin. 2015;33(3):505-516.
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(3):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(6):1677-1687.
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(12): 941–948.
20. Trzepacz PT, Baker RW, Greenhouse J. A symptom rating scale for delirium. *Psychiat Res;* 1998; 23(1): 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(1): 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(5):859-864.
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 (3): 189-198.
24. Kokmen E, Naessens JM, Offord KP. A short test of mental status: Description and preliminary results. *Mayo Clin Proc.* 1987; 62 (4): 281-288.
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 (1): 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(9): 934-9.
27. Donna F, Stroup P, MSc,et al. Berlin S, Sally C. Morton P, Ingram Olkin P, G. David Williamson P, Drummond Rennie M, et al. Meta-analysis of Observational Studies in Epidemiology : A Proposal for Reporting. *JAMA.* 2008;283(15): 2008-1012.

28. BarendregtJJ, Doi SA, Lee YY, et al. Meta-analysis of prevalence. *J Epidemiol Community Health*. 2013;67(11): 974-978.

29. Wong CL, Holroyd-Leduc J, Simel DL, Straus SE. Does this patient have delirium?: value of bedside instruments. *JAMA*. 2010; 304(7):779-786.

30. Laurila JV, Pitkala KH, Strandberg TE, Tilvis RS. The impact of different diagnostic criteria on prevalence rates for delirium. *Dement Geriatr Cogn*. 2003; 16 (3): 156-162.

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

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)

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

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	
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)	**Page 8**
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	
	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)	**Page 9-10**
	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.