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Relationship between hospital or surgeon volume and outcomes in joint arthroplasty: protocol for a suite of systematic reviews and dose-response meta-analyses

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XDW and *WH* conceived and designed the study.

XDW drafted the protocol; *MML*, *YYS*, *ZHZ, QZ*, *JSWK*, *WX*, *TM*, *YH* and *WH* revised the protocol.

XDW and *YYS* will search and select eligible studies; *ZHZ* and *TM* will extract the data, *MML* will check the data; *YH* and *WX* will assess the risk of bias; *QZ* and *JSWK* will perform data synthesis.

XDW and *WH* act as guarantors of the protocol. All the authors approved the publication of the protocol.

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ABSTRACT

Introduction: Joint arthroplasty is a particularly complex orthopedic surgical procedure performed on joints, including the hip, knee, shoulder, ankle, elbow, wrist, and even digit joints. Increasing evidence from volume-outcomes research supports the finding that patients undergoing arthroplasty in high-volume hospitals or by high-volume surgeons achieve better outcomes, and minimum caseload requirements have been established in some areas. However, the relationships between hospital/surgeon volume and outcomes in patients undergoing arthroplasty are not fully understood. Furthermore, whether elective arthroplasty should be restricted to high-volume hospitals or surgeons remains in dispute, and little is known regarding where the thresholds should be set for different types of joint arthroplasties.

Methods and analyses: This is a protocol for a suite of systematic reviews and dose-response meta-analyses, which will be amended and updated in conjunction with the *Preferred Reporting Items for Systematic reviews and Meta-Analysis Protocols* (PRISMA-P). Electronic databases including PubMed, Embase, and The Cochrane Library will be searched for observational studies that examined the relationship between hospital or surgeon volume and clinical outcomes in adult patients undergoing primary or revision of joint arthroplasty. We will use records management software for study selection and a predefined standardized file for data extraction and management. Quality will be assessed using the Newcastle-Ottawa Scale. And meta-analysis, subgroup analysis and sensitivity analysis will be performed using Stata statistical software. Once the volume-outcome relationships are established, we

will examine the potential non-linear relationships between hospital/surgeon volume and outcomes and detect whether thresholds or turning points exist.

Ethics and dissemination: Ethical approval is not required, because these studies are based on aggregated published data. The results of this suite of systematic reviews and meta-analyses will be submitted to peer-reviewed journals for publication.

Trial registration number: This protocol was registered with PROSPERO International Prospective Register for Systematic Reviews (registration number: CRD 42017056639).

Keywords: arthroplasty; hospital volume; surgeon volume; volume-outcome relationship; threshold.

Strengths and limitations of this study

- To the best of our knowledge, this will be the first suite of systematic reviews and dose-response meta-analyses to explore the relationship between hospital/surgeon volume and outcomes in the dominant types of arthroplasties.
- Once the volume-outcome relationships are established, we will examine the potential non-linear relationships between hospital/surgeon volume and outcomes, and determine whether thresholds or turning points exist.
- A comprehensive literature search, developed in consultation with a librarian with experience in systematic review search strategies, will be performed to include all eligible studies to present comprehensive systematic reviews and meta-analyses of the currently available evidence.
- It is highly likely that many studies will be included in the systematic reviews but excluded from the meta-analyses due to a paucity of data, which will introduce some bias.

INTRODUCTION

In previous decades, the relationships between the number of patients treated by a physician/surgeon (physician/surgeon volume) or in a hospital (hospital volume) and patient outcomes have been extensively documented under many medical and surgical conditions.[1,2] In these relationships, patients admitted to a higher volume hospital or treated by a higher volume physician/surgeon are thought to be associated with a lower rate of adverse events and better health outcomes.[3] A posterior definite volume threshold for such an association is usually artificially determined to optimize the correlation when the volume-outcome relationship has been established, indicating that there is a hospital/surgeon volume above which any increase would no longer be associated with improved outcomes. Currently, volume-outcome relationships have been well established in many medical situations and surgical procedures involving cardiac surgery,[4,5] aortic aneurysm repair,[6] critical care,[7,8] and several types of cancer surgery.[9-14] However, controversy pertaining to such volume-outcome relationships persists, and recent published studies have conveyed inconsistent results, thus fuelling a continuing debate.[2]

Supporters believe that volume-outcome relationships may be a sensible surrogate for quality assessment when choosing where to obtain surgical and interventional care,[15] while opponents argue that such volume-outcome relationship are imperfect indicators of healthcare quality, that many studies of volume-outcome relationships are outdated, and that the generalizability of these results is uncertain.[16,17] Despite the heated controversy that it provokes, the volume-outcome

relationship remains a good point of departure in the exploration of optimal care in health services delivery. Understanding these relationships remains critical for clinicians and policymakers because they are under increasing pressure to learn the performance of hospitals/surgeons, analyse the processes of care that lead to optimal outcomes, and identify strategies to improve the quality of care.[18,19] Considering that volume is not an immutable determinant of the incidence of adverse events and that the volume-outcome relationship can change with the development of the healthcare provider and improvements in the quality of care, it should be a priority to update these volume-outcome relationships when new research is released.

Joint arthroplasty, or joint replacement surgery, is a particularly complex orthopedic surgical procedure that is performed when severe joint pain or dysfunction cannot be alleviated by less invasive therapies. The goal of this procedure is to relieve pain, restore joint function, and enhance quality of life.[20-23] Until now, joint arthroplasty has been performed on joints including the hip, knee, shoulder, elbow, wrist, ankle, and even digit joints.

Hip and knee arthroplasties are the most common types of procedures performed.[24] According to estimates, the demand for primary total hip arthroplasty (THA) and revision THA will reach 572,000 and 96,700, respectively, by 2030, while the demand for primary total knee arthroplasty (TKA) and revision TKA will reach 3.48 million and 268,000, respectively.[25,26] Although shoulder arthroplasty is less common than knee and hip arthroplasties, it is still an exceptional procedure with excellent results,[27] and more than 53,000 shoulder arthroplasties are performed each

year in the United States.[28] Because ankle arthrodesis has long been considered the golden standard of surgical treatment for ankle arthritis, total ankle arthroplasty (TAA) is not frequently performed.[29] Only 2608 procedures were performed in the United States in 2010.[30] The elbow joint cannot be easily replaced or bypassed by external aids as can the lower extremity joints, and total elbow arthroplasty (TEA) remains a relatively uncommon surgical procedure.[31,32] Approximately 3000 procedures were performed in the United States in 2015.[33] Similar to the ankle joint, wrist arthrodesis is the most frequently recommended treatment,[34] with only approximately 1000 total wrist arthroplasty (TWA) procedures performed annually in the United States.[35]

The performance of arthroplasty requires not only technically accomplished surgeons to perform relatively complex procedures that require extensive planning, and specialized implants and tools to achieve good intra-operative results, but also expert nurses to provide a complex, well-organized, and technically sophisticated level of peri-operative care.[36] Meanwhile, hospitals that have a high arthroplasty volume also have certain characteristics, including high-efficiency team work, academic medical centre, metropolitan location, and the availability of dedicated resources, such as an operating rooms with special precautions.[37,38] Consequently, relationships between hospital/surgeon volume and clinical outcomes likely exist for patients receiving arthroplasty.

Increasing evidence from volume-outcomes research supports the finding that patients undergoing arthroplasty in high-volume hospitals or by high-volume surgeons achieve better outcomes,[39-49] but the actual definitions of high-volume hospitals and

surgeons are highly variable among studies.[50] To improve clinical outcomes and deliver the best healthcare, the German Federal Joint Committee has established minimum caseload requirements. The committee proposed volume standards for primary TKA are 25 TKAs per year for surgeons and 50 TKAs per year for hospitals.[51] Although accumulating evidence supports these interventions, many researchers question how the minimum caseload requirements should exactly be determined in clinical practice.[50,52]

The relationships between hospital/surgeon volume and outcomes in patients undergoing arthroplasty are not fully understood; whether elective arthroplasty should be restricted to high-volume hospitals or surgeons remains in dispute; and little is known regarding where exactly the thresholds should fall for different types of joint arthroplasties. Considering that this relationship has been extensively documented in the arthroplasty literature, and that previous studies have conveyed inconsistent results, we decided to conduct a suite of systematic reviews and dose-response meta-analyses to address this issue.

OBJECTIVE

This is a protocol for a suite of systematic reviews and dose-response meta-analyses to explore the relationship between hospital/surgeon volume and outcomes in patients undergoing arthroplasty with the following objectives:

(1) to examine the relationships between hospital/surgeon volume and outcomes in different types of joint arthroplasties;

(2) to investigate the dose-response relationship between the volume and outcomes and to propose meaningful hospital/surgeon arthroplasty volume thresholds;

(3) to compare the volume-outcome relationships among different procedure volume for joint arthroplasties (hip and knee arthroplasties *versus* shoulder arthroplasty *versus* ankle and elbow and wrist arthroplasties).

METHODS AND ANALYSIS

Our systematic reviews and meta-analyses will be performed in accordance with guidelines from the *Meta-analysis Of Observational Studies in Epidemiology* (MOOSE) group and the methods prescribed in the *Cochrane Handbook for Systematic Reviews of Interventions*, and will be reported following the *Preferred Reporting Items for Systematic Reviews and Meta-Analyses* (PRISMA) Statement.[53,54]

Registration information

This suite of systematic reviews and dose-response meta-analyses have been registered with the International Prospective Register of Systematic Reviews (PROSPERO CRD42017056639). This protocol will be amended and updated in conjunction with the Preferred Reporting Items for Systematic reviews and Meta-Analysis Protocols (PRISMA-P).[55]

Eligibility criteria

Types of studies

We will include observational studies that examined the relationship between hospital or surgeon volume and clinical outcomes, mainly including prospective cohort studies,

retrospective cohort studies, case-control studies, and cross-sectional studies, and meeting abstracts will also be included if eligible. There will be no restrictions regarding publication status or language.

Types of participants

Adult patients undergoing primary or revision joint arthroplasty will be included, with a focus on primary and revision THA, primary and revision TKA, and shoulder, elbow, ankle or wrist arthroplasty.

Types of outcome measures

Outcomes of interest for this suite of systematic reviews and meta-analyses are as follows: rate of mortality, readmission, complication, dislocation, and revision, as well as wound infection, urinary tract infection, length of hospital stay, hospitalization cost, and functional score. The list is not exhaustive and will be modified based on the evidence compiled from the systematic reviews. We will not exclude studies based on outcomes and we will present these findings in a separate section for systematic reviews.

Information sources

We will search the electronic bibliographic databases: PubMed, Embase, and The Cochrane Library from inception to March, 2018 to ensure that all the recent relevant studies are captured. No language restrictions will be imposed. In addition, we will search the clinical trial registry for ongoing and unpublished studies. Reference lists of all the identified studies as well as relevant reviews will be manually searched for potentially relevant studies. Potential grey literature sources (e.g. conference abstracts)

will be screened to identify any eligible published and unpublished studies.

Search strategy

Electronic search terms performed for each part included both exploded Medical Subject Headings (MeSH) terms and corresponding keywords. Search terms will include those related to 'Volume', 'Caseload', 'Arthroplasty', 'Replacement', and their variants. The search will be broad, and no restrictions will be applied. After retrieving and combining the corresponding subject terms using 'OR', the two parts were combined using 'AND'. The detailed librarian-assisted search strategy of PubMed is shown in **Table 1**. The computerized literature search of other databases will also be performed using this strategy.

Data collection and synthesis

Study selection

The obtained study records will be exported from medical databases and imported into a software package (EndNote version X7, Thomson Reuters, CA, USA) for records management. We will use a three-stage process for study screening and selection using standardized and piloted screening forms (**Figure 1**). First, two reviewers (XDW, YYS) will jointly remove duplicate records from the initial searched results; Second, the two reviewers will independently screen the titles and abstracts of each records to determine the eligibility, and identified as included, excluded or requiring further assessment. Third, full-text of potentially eligible records were retrieved and reviewed independently with reference to the predetermined inclusion and exclusion criteria. Differences of opinions will be resolved by discussion and

consensus with a third reviewer (WH).

Data extraction and management

A predefined standardized Excel (Microsoft Corporation, WA, USA) file will be applied for data extraction, and separate sheets will be applied for each type of the arthroplasty. Two independent reviewers (ZHZ, YH) will extract the following information from each included study: first author, publication year, study location, study design, database, study period, number of patients, volume grouping and category, multivariate effect estimate, covariates in the fully adjusted model, wound infection, urinary tract infection, length of hospital stay, hospitalization cost, and functional scores, as well as rate of mortality, readmission, complication, dislocation, and revision. The supplementary files of the included studies will also be examined for data extraction. In cases of missing data, we will contact the authors of the study. If we fail to obtain the missing data, the study will not be included in data analysis. Any discrepancies between the two reviewers will be resolved through consensus by discussion with an independent adjudicator (WH) as required.

Quality assessment

As recommended by the MOOSE checklist, the quality of the included studies will be assessed using the Newcastle-Ottawa Scale, which is a validated scale for evaluating the quality of non-randomized studies in meta-analyses. This scale contains eight items with a maximum score of nine stars, which are awarded based on three domains: four stars for selection, two stars for comparability, and three stars for outcomes. We

will assign studies with scores of 0~3, 4~6, and 7~9 as low-, moderate-, and high-quality studies, respectively. Two authors (MT, WX) will independently perform the quality appraisal, and disagreements will be resolved by a third investigator (WH).

Data synthesis

Included studies that provide sufficient data to calculate an effect size measure will be included in the quantitative analysis. To quantify the degree of heterogeneity across the studies, we will use the Cochrane's Q test with its *P* values and the Higgins I^2 statistic with its 95% confidence intervals (CIs).[56,57] The I^2 statistic is used to quantify the proportion of total variation in the effect estimation that is due to between-study variation. An I^2 values of 25%, 50%, and 75% will be used as indicators of low, moderate and high heterogeneity, respectively.[57,58] Multivariate odds ratios (ORs) with corresponding 95% CIs between extreme levels of hospital/surgeon volume (highest versus lowest) will be pooled using a random-effects model accounting for clinical heterogeneity. For the possible presence of publication bias, we will evaluate by using a funnel plot for meta-analyses including at least 10 studies.[59] We will also use tests proposed by Egger and colleagues, and by Begg and Mazumdar to measure funnel plot asymmetry.[60,61]

Subgroup analysis and Sensitivity analysis

To explore the potential sources of heterogeneity among the studies and to test the robustness of the volume-outcome relationships, we will further carry out subgroup analyses, primarily including the study design (cohort studies *versus* cross-sectional

studies), volume grouping (tertiles *versus* quartiles *versus* quintiles), adjusted factors (uncertain), sample size (uncertain) and period (?-1998 *versus* 1999-2008 *versus* 2009-2018). Additional 'leave-one-out' sensitivity analyses will be performed to explore whether the results were dominated by a single study; this will be investigated by omitting each study in turn and examining the influence of each individual study on the overall risk estimate (the "leave-one-out" approach). This approach will enable an evaluation of the influence of individual studies on the overall risk estimate, and a two-sided *P* value < 0.05 will be considered as statistically significant. All the above analyses will be performed using Stata statistical software version 13.0 (StataCorp, College Station, TX, USA).

Dose-Response analysis and Threshold Effect analysis

Once the volume-outcome relationships are established, we will use two-step random-effects meta-regression models to examine potential non-linear relationships between hospital/surgeon volume and outcomes. To derive the dose-response curve, study-specific slopes (non-linear trends) with 95% CIs from the natural logs of the reported ORs and CIs across the categories of hospital/surgeon volume would be calculated. The details of the methods that will be used have been described by Greenland and Orsini et al.[62,63] In particular, the mean or median level of volume for each category of annual hospital/surgeon volume would be assigned to each corresponding OR for each study. If the data are not available, we will assign the midpoint of the upper and lower boundaries in each category as the annual

hospital/surgeon volume. In cases where the upper or lower boundary of the category is open-ended or extreme upper or lower values are present, we will assume that the absent boundary has the same amplitude as the adjacent category, meaning that the highest boundary has the same amplitude as the closest category, and the lowest boundary will be assumed to be zero. Additionally, only studies that report the number of events and control subjects (rather than the event rate), and the OR and its variance estimate for at least three categories will be eligible for dose-response analysis.

For different types of arthroplasties, if the dose-response relationships are available, we will further develop a two-piecewise linear regression model to detect whether there exist thresholds or turning points of the annual hospital/surgeon volume on outcome using a smoothing function. The threshold level will be determined using trial and error, primarily by including the selection of turning points along a predefined interval, and choosing the turning point that yields the maximum model likelihood. All analyses will be performed using Empower (R) (www.empowerstats.com, X&Y solutions, Inc., MA, USA).

DISCUSSION

The relationship between hospital/surgeon volume and clinical outcomes has been proposed in arthroplasty for more than two decades.[39] Although dozens of studies have been published and reported conflicting results, dose-response meta-analyses

have not been performed to systematically and quantitatively evaluate the volume-outcome relationships, and meaningful thresholds for "low" and "high" levels have not been established for hospital/surgeon volume. Nonetheless, minimum caseload requirements or certificate-of-need programmes have been implemented to improve healthcare quality or to prevent the overutilization of healthcare resources. These measures are intended to align the supply of facilities with demand, but the advantages and disadvantages of regionalization or centralization in joint arthroplasty have not been fully elaborated.

Our overall aim is to perform a suite of systematic reviews and dose-response meta-analyses to explore the relationship between hospital/surgeon volume and outcomes for the dominant types of arthroplasties. Considering the annualized surgical volumes, we will separate joint arthroplasties as hip and knee arthroplasties, shoulder arthroplasty, and ankle, elbow and wrist arthroplasties. Primarily due to the dramatic variation in these volumes, different volume-outcome relationships and thresholds will likely be found. This suite of systematic reviews and meta-analyses will provide new knowledge that is essential for healthcare service planning as well as knowledge on the process of implementation or adjustment of programmes to improve the quality of care.

We anticipate challenges in conducting this research. First, it is highly likely that many studies will be included in the systematic reviews but excluded from the meta-analyses due to a paucity of data, which will introduce some bias. Second, most

of the included studies will be retrospective, which will limit the ability to control for confounders. Additionally, the numbers of eligible studies for ankle, elbow, and wrist arthroplasties are predicted to be small, and the findings of the meta-analyses may be restricted.

ETHICS AND DISSEMINATION

Ethics

Because this suite of systematic reviews and dose-response meta-analyses involves analysis of secondary data that are anonymous, are available in the public domain, and does not involve human participants or encroach on the privacy of individual patients, ethical approval is not required.

Dissemination

The results of this suite of systematic reviews and dose-response meta-analyses will be disseminated in peer-reviewed journals. The findings of these studies will also be shared with all stakeholders. Knowledge dissemination workshops will be conducted with relevant stakeholders to transfer the evidence, which will be tailored to the stakeholder (e.g., policy briefs, publications, information booklets, etc.).

Table 1 Search strategy for PubMed

Search	Query
#1	"Arthroplasty"[Mesh]
#2	Arthroplasty[Title/Abstract]
#3	Replacement[Title/Abstract]
#4	"Arthroplasty, Replacement"[Mesh]
#5	#1 OR #2 OR #3 OR #4
#6	"Hospitals, High-Volume"[Mesh]
#7	"Hospitals, Low-Volume"[Mesh]
#8	Volume[Title/Abstract]
#9	Volumes[Title/Abstract]
#10	Caseload[Title/Abstract]
#11	Caseloads[Title/Abstract]
#12	#6 OR #7 OR #8 OR #9 OR #10 OR #11
#13	hemofiltration[Title/Abstract]
#14	hematoma[Title/Abstract]
#15	Brain[Title/Abstract]
#16	Blood[Title/Abstract]
#17	Search Platelet[Title/Abstract]
#18	Gastric[Title/Abstract]
#19	Ventricule[Title/Abstract]
#20	Pressure[Title/Abstract]
#21	Lung[Title/Abstract]
#22	Stroke[Title/Abstract]
#23	hemodialysis[Title/Abstract]
#24	Tidal[Title/Abstract]
#25	#12 NOT #13 NOT #14 NOT #15 NOT #16 NOT #17 NOT #18 NOT #19 NOT #20 NOT #21 NOT #22 NOT #23 NOT #24
#26	#12 AND #25

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Figure legends

Figure 1. PRISMA flow diagram showing the process of literature screening, study selection, and reasons for study exclusion. The PRISMA statement is used worldwide to improve the reporting of systematic reviews and meta-analyses.

PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses.

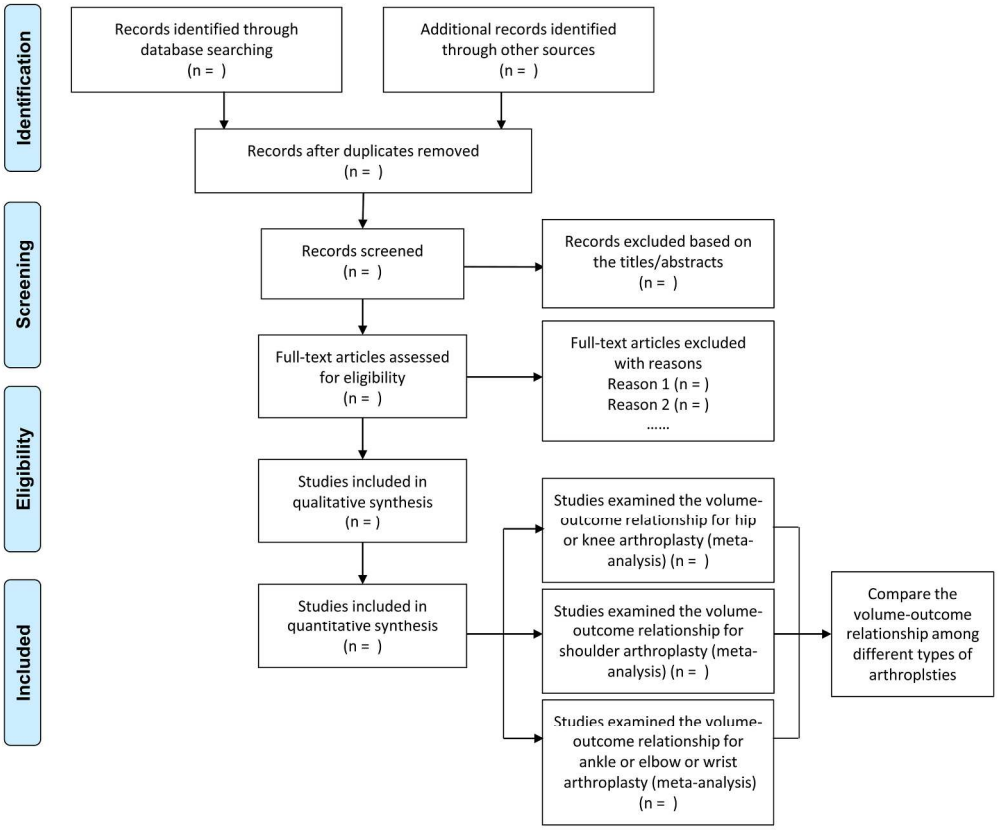

Figure 1. PRISMA flow diagram showing the process of literature screening, study selection, and reasons for study exclusion. The PRISMA statement is used worldwide to improve the reporting of systematic reviews and meta-analyses. PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses.

242x201mm (300 x 300 DPI)

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 no.
ADMINISTRATIVE INFORMATION			
Title:			
Identification	1a	Identify the report as a protocol of a systematic review	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	
Authors:			
Contact	3a	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author	1-2
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review	2
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	N/A
Support:			
Sources	5a	Indicate sources of financial or other support for the review	2
Sponsor	5b	Provide name for the review funder and/or sponsor	N/A
Role of sponsor or funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol	N/A
INTRODUCTION			
Rationale	6	Describe the rationale for the review in the context of what is already known	6-9
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	9-10
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	10-11
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	11-12
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	12, Table1

		repeated	
Study records:			
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	13-15
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)	12-13, Figure1
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	13
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	13
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	13
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	13-14
Data synthesis	15a	Describe criteria under which study data will be quantitatively synthesised	14-15
	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)	12
	15c	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression)	14-17
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned	11
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies)	14
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (such as GRADE)	No

*** 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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Relationship between hospital or surgeon volume and outcomes in joint arthroplasty: protocol for a suite of systematic reviews and dose-response meta-analyses

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Relationship between hospital or surgeon volume and outcomes in joint arthroplasty: protocol for a suite of systematic reviews and dose-response meta-analyses

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Author contributions:

XDW and *WH* conceived and designed the study.

XDW drafted the protocol; *MML*, *YYS*, *ZHZ, QZ*, *JSWK*, *WX*, *TM*, *YH* and *WH* revised the protocol.

XDW and *YYS* will search for and select eligible studies; *ZHZ* and *TM* will extract the data, *MML* will check the data; *YH* and *WX* will assess the risk of bias; *QZ* and *JSWK* will perform the data synthesis.

XDW and *WH* act as guarantors of the protocol. All authors approved the publication of the protocol.

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ABSTRACT

Introduction: Joint arthroplasty is a particularly complex orthopaedic surgical procedure performed on joints, including the hip, knee, shoulder, ankle, elbow, wrist, and even digit joints. Increasing evidence from volume-outcomes research supports the finding that patients undergoing arthroplasty in high-volume hospitals or by high-volume surgeons achieve better outcomes, and minimum caseload requirements have been established in some areas. However, the relationships between hospital/surgeon volume and outcomes in patients undergoing arthroplasty are not fully understood. Furthermore, whether elective arthroplasty should be restricted to high-volume hospitals or surgeons remains in dispute, and little is known regarding where the thresholds should be set for different types of joint arthroplasties.

Methods and analyses: This is a protocol for a suite of systematic reviews and dose-response meta-analyses, which will be amended and updated in conjunction with the *Preferred Reporting Items for Systematic reviews and Meta-Analysis Protocols* (PRISMA-P). Electronic databases, including PubMed and Embase, will be searched for observational studies examining the relationship between the hospital or surgeon volume and clinical outcomes in adult patients undergoing primary or revision of joint arthroplasty. We will use records management software for study selection and a predefined standardized file for data extraction and management. Quality will be assessed using the Newcastle-Ottawa Scale, and the meta-analysis, subgroup analysis and sensitivity analysis will be performed using Stata statistical software. Once the volume-outcome relationships are established, we will examine the potential

non-linear relationships between hospital/surgeon volume and outcomes and detect whether thresholds or turning points exist.

Ethics and dissemination: Ethical approval is not required, because these studies are based on aggregated published data. The results of this suite of systematic reviews and meta-analyses will be submitted to peer-reviewed journals for publication.

Trial registration number: This protocol was registered with PROSPERO International Prospective Register for Systematic Reviews (registration number: CRD 42017056639).

Keywords: arthroplasty; hospital volume; surgeon volume; volume-outcome relationship; threshold.

Strengths and limitations of this study

- To the best of our knowledge, this study will be the first suite of systematic reviews and dose-response meta-analyses to explore the relationship between the hospital/surgeon volume and outcomes of the dominant types of arthroplasties.
- Once the volume-outcome relationships are established, we will examine the potential non-linear relationships between hospital/surgeon volume and outcomes, and determine whether thresholds or turning points exist.
- A comprehensive literature search, developed in consultation with a librarian with experience in systematic review search strategies, will be performed to include all eligible studies to present comprehensive systematic reviews and meta-analyses of the currently available evidence.
- It is highly likely that many studies will be included in the systematic reviews but excluded from the meta-analyses due to a paucity of data, which will introduce some bias.

INTRODUCTION

In previous decades, the relationships between the number of patients treated by a physician/surgeon (physician/surgeon volume) or in a hospital (hospital volume) and patient outcomes have been extensively documented under many medical and surgical conditions.[1-14] In these relationships, patients admitted to a higher volume hospital or treated by a higher volume physician/surgeon are thought to be associated with a lower rate of adverse events and better health outcomes.[3] And a posteriori defined volume threshold for such an association usually is artificially determined to optimize the correlation when the volume-outcome relationship has been established, indicating that there is a hospital/surgeon volume above which any increase will no longer be associated with improved outcomes. However, controversy pertaining to such volume-outcome relationships persists, and recent published studies have conveyed inconsistent results, thus fuelling a continuing debate.[2]

Supporters believe that volume-outcome relationships may be a sensible surrogate for quality assessment when choosing where to obtain surgical and interventional care,[15] while opponents argue that such volume-outcome relationships are imperfect indicators of healthcare quality and that generalizability of these results is uncertain.[16,17] Despite the heated controversy that it provokes, the volume-outcome relationship remains a good point of departure in the exploration of optimal care in health services delivery. Understanding these relationships remains critical for clinicians and policymakers because they are under increasing pressure to elucidate the performances of hospitals/surgeons, analyse the processes of care that lead to

optimal outcomes, and identify strategies to improve the quality of care.[18,19] Considering that volume is not an immutable determinant of the incidence of adverse events and that the volume-outcome relationship can change with the development of the healthcare provider and improvements in the quality of care, updating these volume-outcome relationships should be a priority when new research released.

Joint arthroplasty, or joint replacement surgery, is a particularly complex orthopaedic surgical procedure that is performed when severe joint pain or dysfunction cannot be alleviated by less invasive therapies. The goal of this procedure is to relieve pain, restore joint function, and enhance quality of life.[20-23] Until now, joint arthroplasty has been performed on joints including the hip, knee, shoulder, elbow, wrist, ankle, and even digit joints.

Hip and knee arthroplasties are the most common types of procedures performed.[24] According to estimates for the United States, the demands for primary total hip arthroplasty (THA) and revision THA will reach 572,000 and 96,700, respectively, by 2030, while the demands for primary total knee arthroplasty (TKA) and revision TKA will reach 3.48 million and 268,000, respectively.[25,26] Although shoulder arthroplasty is less common than knee and hip arthroplasties, it is still an exceptional procedure with excellent results,[27] and more than 53,000 shoulder arthroplasties are performed each year in the United States.[28] Because ankle arthrodesis has long been considered the gold standard of surgical treatment for ankle arthritis, total ankle arthroplasty (TAA) is not frequently performed.[29] Only 2608 procedures were performed in the United States in 2010.[30] The elbow joint cannot be

easily replaced or bypassed by external aids as can the lower extremity joints, and total elbow arthroplasty (TEA) remains a relatively uncommon surgical procedure.[31,32] Approximately 3000 procedures were performed in the United States in 2015.[33] Similar to the ankle joint, wrist arthrodesis is the most frequently recommended treatment,[34] with only approximately 1000 total wrist arthroplasty (TWA) procedures performed annually in the United States.[35]

Increasing evidence from volume-outcome research supports the finding that patients undergoing arthroplasty in high-volume hospitals or by high-volume surgeons achieve better outcomes,[36-49] but the actual definitions of high-volume hospitals and surgeons are highly variable among studies.[50] To improve clinical outcomes and deliver the best healthcare, the German Federal Joint Committee has established minimum caseload requirements. The volume standards for primary TKA proposed by the Committee are 25 TKAs per year for surgeons and 50 TKAs per year for hospitals.[51] Although accumulating evidence supports these interventions, many researchers question how the minimum caseload requirements should be exactly determined in clinical practice.[50,52]

The relationships between the hospital/surgeon volume and the outcomes in patients undergoing arthroplasty are not fully understood; whether elective arthroplasty should be restricted to high-volume hospitals or surgeons remains in dispute; and little is known regarding where exactly the thresholds should fall for different types of joint arthroplasties. Therefore, we decided to explore the volume-outcome relationships and thresholds to address this issue.

OBJECTIVE

This is a protocol for a suite of systematic reviews and dose-response meta-analyses to explore the relationship between hospital/surgeon volume and outcomes in patients undergoing arthroplasty with the following objectives:

(1) to examine the relationships between hospital/surgeon volume and outcomes in different types of joint arthroplasties;

(2) to investigate the dose-response relationship between the volume and outcomes and to propose meaningful hospital/surgeon arthroplasty volume thresholds;

(3) to compare the volume-outcome relationships among different procedure volumes for joint arthroplasties (primary hip and knee arthroplasties *versus* revision hip and knee arthroplasties *versus* shoulder arthroplasty *versus* ankle, elbow, and wrist arthroplasties).

METHODS AND ANALYSIS

Our systematic reviews and meta-analyses will be performed in accordance with guidelines from the *Meta-analysis Of Observational Studies in Epidemiology* (MOOSE) group and the methods prescribed in the *Cochrane Handbook for Systematic Reviews of Interventions* and will be reported following the *Preferred Reporting Items for Systematic Reviews and Meta-Analyses* (PRISMA) Statement.[53,54]

Registration information

This suite of systematic reviews and dose-response meta-analyses has been registered

with the International Prospective Register of Systematic Reviews (PROSPERO CRD42017056639). This protocol will be amended and updated in conjunction with the *Preferred Reporting Items for Systematic reviews and Meta-Analysis Protocols* (PRISMA-P).[55]

Eligibility criteria

Types of studies

We will include observational studies that examined the relationship between hospital or surgeon volume and clinical outcomes, mainly including prospective cohort studies, retrospective cohort studies, case-control studies, and cross-sectional studies, and meeting abstracts will also be included if eligible. There will be no restrictions regarding publication status or language.

Types of participants

Adult patients undergoing primary or revision joint arthroplasty will be eligible, and will specifically include those undergoing primary and revision THA, primary and revision TKA, and primary shoulder, elbow, ankle or wrist arthroplasty.

Types of outcome measures

The outcomes of interest are as follows: rate of mortality, readmission, periprosthetic joint infection, dislocation, revision, as well as wound complication, urinary tract infection, length of hospital stay, hospitalization cost, and functional score. The list is not exhaustive and will be modified based on the evidence compiled from the systematic reviews. We will not exclude studies due to paucity of data and we will include these studies in systematic reviews.

Patient and public involvement

In this study, data will not be collected directly from patients but instead will be obtained from published studies available in the main databases. Therefore, patients will not be involved in the completion of the systematic review protocol or subsequent research.

Information sources

We will search the electronic bibliographic databases PubMed and Embase from inception to March 2018 to ensure that all recent relevant studies are captured. No language restrictions will be imposed. In addition, we will search the clinical trial registry for ongoing and unpublished studies. Reference lists of all the identified studies as well as relevant reviews will be manually searched for potentially relevant studies. Potential grey literature sources (e.g., conference abstracts) will be screened to identify any eligible published and unpublished studies.

Search strategy

Electronic search terms for each part will include both exploded Medical Subject Headings (MeSH) terms and corresponding keywords. Search terms will include those related to 'Volume', 'Caseload', 'Arthroplasty', 'Replacement', and their variants. The search will be broad, and no restrictions will be applied. After retrieving and combining the corresponding subject terms using 'OR', the two parts will be combined using 'AND'. The detailed librarian-assisted search strategy is shown in **Table 1**.

Data collection and synthesis

Study selection

The obtained study records will be exported from medical databases and imported into a software package (EndNote version X7, Thomson Reuters, CA, USA) for records management. We will use a three-stage process for study screening and selection using standardized and piloted screening forms (**Figure 1**). First, two reviewers (XDW and YYS) will jointly remove duplicate records from the initial search results; Second, the two reviewers will independently screen the titles and abstracts of each record to determine the eligibility, and identify the studies as included, excluded, or requiring further assessment. Third, the full text of potentially eligible records will be retrieved and reviewed independently with reference to the predetermined inclusion and exclusion criteria. Differences of opinions will be resolved by discussion and consensus with a third reviewer (WH).

Data extraction and management

A predefined standardized Excel (Microsoft Corporation, WA, USA) file will be applied for data extraction, and separate sheets will be applied for each type of arthroplasty. Two independent reviewers (ZHZ and YH) will extract the following information from each included study: first author, publication year, study location, study design, database, study period, number of patients, volume grouping and category, multivariate effect estimate, covariates in the fully adjusted model, as well as outcome measures mentioned above. The supplementary files of the included studies will also be examined for data extraction. In cases of missing data, we will contact the authors of the study. If we fail to obtain the missing data, the study will

not be included in data analysis. Any discrepancies between the two reviewers will be resolved through consensus by discussion with an independent adjudicator (WH) as required.

Quality assessment

As recommended by the MOOSE checklist, the quality of the included studies will be assessed using the Newcastle-Ottawa Scale, which is a validated scale for evaluating the quality of non-randomized studies in meta-analyses. This scale contains eight items with a maximum score of nine stars, which are awarded based on three domains: four stars for selection, two stars for comparability, and three stars for outcomes. We will assign studies with scores of 0~3, 4~6, and 7~9 as low-, moderate-, and high-quality studies, respectively. Two authors (MT and WX) will independently perform the quality appraisal, and disagreements will be resolved by a third investigator (WH).

Data synthesis

Included studies that provide sufficient data to calculate an effect size measure will be included in the quantitative analysis. To quantify the degree of heterogeneity across studies, we will use Cochrane's Q test with its *P* values and the Higgins I^2 statistic with its 95% confidence intervals (CIs).[56,57] The I^2 statistic is used to quantify the proportion of total variation in the effect estimation that is due to between-study variation. I^2 values of 25%, 50%, and 75% will be used as indicators of low, moderate, and high heterogeneity, respectively.[57,58] Multivariate odds ratios (ORs) with corresponding 95% CIs between extreme levels of hospital/surgeon volume (highest

versus lowest) will be pooled using a random-effects model accounting for clinical heterogeneity. We will evaluate the possible presence of publication bias by using a funnel plot for meta-analyses including at least 10 studies.[59] We will also use tests proposed by Egger and colleagues, and by Begg and Mazumdar to measure funnel plot asymmetry.[60,61]

Subgroup analysis and sensitivity analysis

To explore the potential sources of heterogeneity among the studies and to test the robustness of the volume-outcome relationships, we will further carry out subgroup analyses, primarily including the study design (cohort studies *versus* cross-sectional studies), adjusted factors (uncertain), sample size (uncertain) and period (?-1998 *versus* 1999-2008 *versus* 2009-2018). Additional 'leave-one-out' sensitivity analyses will be performed to explore whether the results are dominated by a single study; this issue will be investigated by omitting each study in turn and examining the influence of each individual study on the overall risk estimate (the "leave-one-out" approach). This approach will enable an evaluation of the influence of individual studies on the overall risk estimate, and a two-sided P value < 0.05 will be considered as statistically significant. All of the above analyses will be performed using the Stata statistical software version 13.0 (StataCorp, College Station, TX, USA).

Dose-response analysis and threshold Effect analysis

Once the volume-outcome relationships are established, we will use two-step

random-effects meta-regression models to examine potential non-linear relationships between hospital/surgeon volume and outcomes. To derive the dose-response curve, study-specific slopes (non-linear trends) with 95% CIs from the natural logs of the reported ORs and CIs across the hospital/surgeon volume categories will be calculated. The details of the methods that will be used have been described by Greenland and Orsini et al.[62,63] In particular, the mean or median level of volume for each category of the annual hospital/surgeon volume will be assigned to each corresponding OR for each study. If the data are not available, we will assign the midpoint of the upper and lower boundaries in each category as the annual hospital/surgeon volume. In cases where the upper or lower boundary of the category is open-ended or extreme upper or lower values are present, we will assume that the absent boundary has the same amplitude as the adjacent category, meaning that the highest boundary has the same amplitude as the closest category, and the lowest boundary will be assumed to be zero. Additionally, only studies that report the number of events and control subjects (rather than the event rate), and the OR and its variance estimate for at least three categories will be eligible for the dose-response analysis.

For different types of arthroplasties, if the dose-response relationships are available, we will further develop a two-piecewise linear regression model to detect whether there exist thresholds or turning points of the annual hospital/surgeon volume on outcome using a smoothing function. The threshold level will be determined using trial and error, primarily by including the selection of turning points along a predefined interval and choosing the turning point that yields the maximum model

likelihood. All analyses will be performed using Empower (R) (www.empowerstats.com, X&Y solutions, Inc., MA, USA).

DISCUSSION

The relationship between hospital/surgeon volume and clinical outcomes has been proposed in arthroplasty for more than two decades.[39] Currently, minimum caseload requirements or certificate-of-need programmes have been implemented to improve healthcare quality or to prevent overutilization of healthcare resources. These measures are intended to align the supply of facilities with demand, but the advantages and disadvantages of regionalization or centralization in joint arthroplasty have not been fully elaborated. Therefore, this suite of systematic reviews and meta-analyses will provide new knowledge that is essential for healthcare service planning as well as knowledge on the implementation process or adjustment of programmes to improve the quality of care.

We anticipate challenges in conducting this research. First, it is highly likely that many studies will be included in the systematic reviews but excluded from the meta-analyses due to a paucity of data, which will introduce some bias. Second, most of the included studies will be retrospective, which will limit the ability to control for confounders. Additionally, the numbers of eligible studies for ankle, elbow, and wrist arthroplasties are predicted to be small, and the findings of the meta-analyses may be

restricted.

ETHICS AND DISSEMINATION

Ethics

Because this suite of systematic reviews and dose-response meta-analyses involves analysis of anonymous secondary data that are available in the public domain, and does not involve human participants or encroach on the privacy of individual patients, ethical approval is not required.

Dissemination

The findings will be disseminated in peer-reviewed journals and will also be shared with all stakeholders. Knowledge dissemination workshops will be conducted with relevant stakeholders to transfer the evidence, which will be tailored to the stakeholder (e.g., policy briefs, publications, and information booklets).

Table 1 Search strategy

PubMed	Search	Query
	#1	"Arthroplasty"[Mesh]
	#2	Arthroplasty[Title/Abstract]
	#3	Replacement[Title/Abstract]
	#4	"Arthroplasty, Replacement"[Mesh]
	#5	#1 OR #2 OR #3 OR #4
	#6	"Hospitals, High-Volume"[Mesh]
	#7	"Hospitals, Low-Volume"[Mesh]
	#8	Volume[Title/Abstract]
	#9	Volumes[Title/Abstract]
	#10	Caseload[Title/Abstract]
	#11	Caseloads[Title/Abstract]
	#12	#6 OR #7 OR #8 OR #9 OR #10 OR #11
	#13	hemofiltration[Title/Abstract]
	#14	hematoma[Title/Abstract]
	#15	Brain[Title/Abstract]
	#16	Blood[Title/Abstract]
	#17	Search Platelet[Title/Abstract]
	#18	Gastric[Title/Abstract]
	#19	Ventricule[Title/Abstract]
	#20	Pressure[Title/Abstract]
	#21	Lung[Title/Abstract]
	#22	Stroke[Title/Abstract]
	#23	hemodialysis[Title/Abstract]
	#24	Tidal[Title/Abstract]
	#25	#12 NOT #13 NOT #14 NOT #15 NOT #16 NOT #17 NOT #18 NOT #19 NOT #20 NOT #21 NOT #22 NOT #23 NOT #24
	#26	#12 AND #25
Embase	**Search**	**Query**
	#1	arthroplasty'/exp
	#2	replacement arthroplasty'/exp
	#3	arthroplasty:ti,ab
	#4	replacement:ti,ab
	#5	#1 OR #2 OR #3 OR #4
	#6	volume'/exp
	#7	volume:ti,ab
	#8	volumes:ti,ab
	#9	caseload:ti,ab

#10	caseloads:ti,ab
#11	#6 OR #7 OR #8 OR #9 OR #10
#12	hemofiltration:ti,ab
#13	hematoma:ti,ab
#14	brain:ti,ab
#15	blood:ti,ab
#16	platelet:ti,ab
#17	gastric:ti,ab
#18	ventricule:ti,ab
#19	pressure:ti,ab
#20	lung:ti,ab
#21	stroke:ti,ab
#22	hemodialysis:ti,ab
#23	tidal:ti,ab
#24	#12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23
#25	#11 NOT #24
#26	#5 AND #25

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Figure legends

Figure 1. PRISMA flow diagram showing the process of literature screening, study selection, and reasons for study exclusion. The PRISMA statement is used worldwide to improve the reporting of systematic reviews and meta-analyses.

PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses.

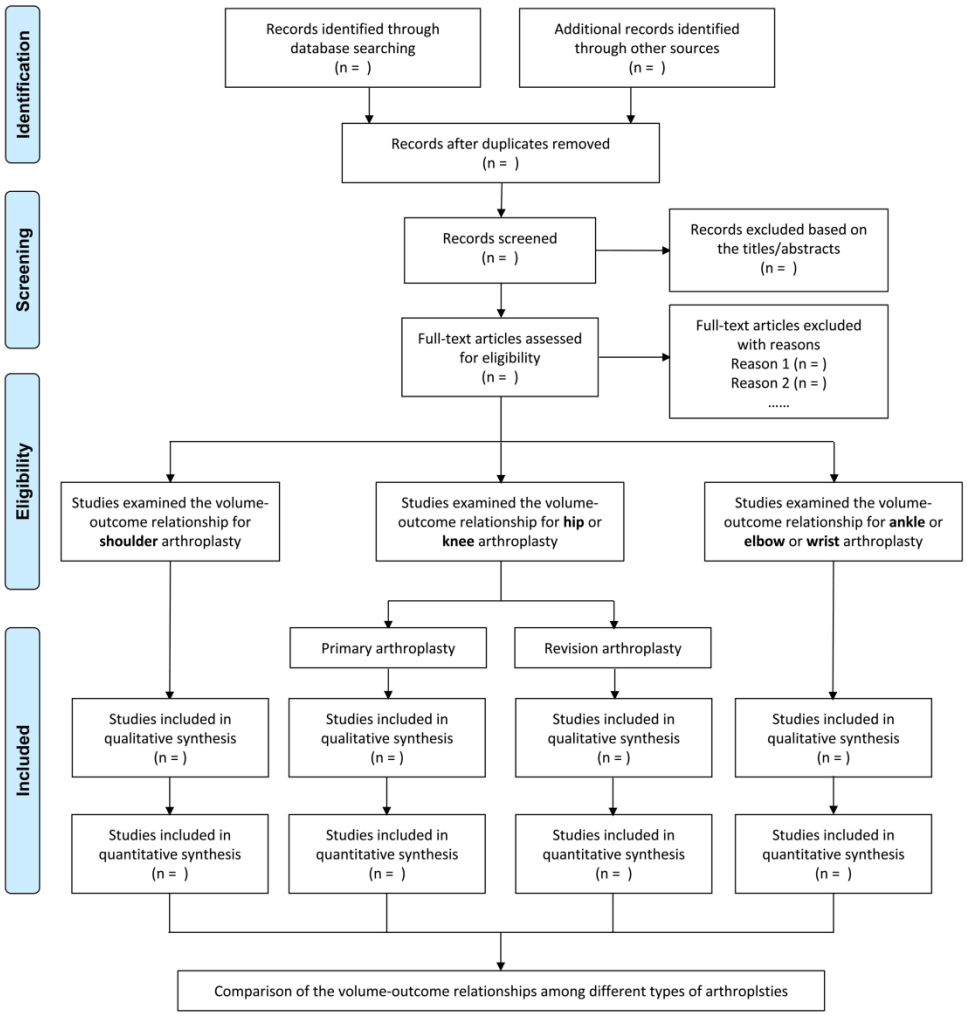

Figure 1. PRISMA flow diagram showing the process of literature screening, study selection, and reasons for study exclusion. The PRISMA statement is used worldwide to improve the reporting of systematic reviews and meta-analyses.

252x262mm (300 x 300 DPI)

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 no.
ADMINISTRATIVE INFORMATION			
Title:			
Identification	1a	Identify the report as a protocol of a systematic review	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	CRD 42017056639
Authors:			
Contact	3a	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author	1-2
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review	2
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	N/A
Support:			
Sources	5a	Indicate sources of financial or other support for the review	2
Sponsor	5b	Provide name for the review funder and/or sponsor	**No sponsor**
Role of sponsor or funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol	**No sponsor or funder**
INTRODUCTION			
Rationale	6	Describe the rationale for the review in the context of what is already known	6-8
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	9
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	10-11
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	11

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	11, Table1
Study records:			
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	12-15
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)	12, Figure1
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	12-13
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	12-13
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	10, 12-13
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	13-14
Data synthesis	15a	Describe criteria under which study data will be quantitatively synthesised	13-15
	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)	13
	15c	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression)	14-16
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned	10
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies)	13-14
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (such as GRADE)	No

*** 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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