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Study protocol

Title:

Avalanche of systematic reviews on the same topic in surgery: a study protocol for a meta-epidemiological investigation

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ABSTRACT

Introduction:

We are witnessing an explosive increase in redundant and overlapping publications of systematic review and meta-analyses (SRs/MAs) on the same topic, which often present conflicting results and interpretations, in the current medical literature. They represent wasted efforts on the part of investigators and peer reviewers and may confuse and possibly mislead clinicians and policymakers. Here, we present a protocol for a meta-epidemiological investigation to describe how often there are overlapping SRs/MAs on the same topic, to assess the quality of these multiple publications, and to investigate the causes of discrepant results between multiple SRs/MAs in the field of major surgery.

Methods and analysis:

We will use MEDLINE/PubMed to identify all SRs/MAs of randomized controlled trials (RCTs) published in 2015 regarding major surgical interventions. After identifying the "benchmark" SRs/MAs published in 2015, a manual hand-search will be carried out to identify the previous SRs/MAs on the same topic that were published within 5 years of the "benchmark" SRs/MAs. We will tabulate the number of previous SRs/MAs on the same topic, and then describe their variations in numbers of RCTs included, sample sizes, effect size estimates and other characteristics. We will also assess the differences in quality of each SRs/MAs using the AMSTAR score. Finally, we will investigate the potential reasons to explain the discrepant results between multiple SRs/MAs.

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No formal ethical approval and informed consent are required because this study will not collect primary individual data. The intended audiences of the findings include clinicians, healthcare researchers, and policymakers. We will publish our findings as a scientific report in a peer-reviewed journal.

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Strengths and limitations of this study

- This meta-epidemiological study is the first to focus on the cause of discrepant results between multiple overlapping SRs/MAs on many and unspecified topics in surgery.
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INTRODUCTION

Description of the condition

In recent years, the number of published systematic reviews (SRs) and meta-analyses (MAs) have been increasing explosively in many medical fields.[1-4] When a small number of randomized control trials (RCTs) of new research questions are published, new SRs/MAs soon follow these RCTs. Indeed, it is becoming more and more difficult to find a new research question that nobody has examined as a systematic review article in medical journals. Furthermore, many topics addressed by SRs/MAs often overlap with each other entirely or partially, and instances have been reported where more than 10 SRs/MAs were published on a single topic in a limited span of time.[2-3] These potentially redundant publications may represent duplicated efforts for researchers, peer reviewers, and editors of the medical journals.

The picture is even more confusing and distressing for readers of the medical literature. Some previous studies have shown that the numbers of pooled RCTs and included patient' sample sizes are quite different across SRs/MAs on the same topic.[2,3,5-10] It is then a natural consequence that there are discrepancies between results of SRs/MAs; different effect sizes, with different statistical precision, and even different directions of effect have been reported.[2,3,5-10] Such conflicting results can confuse and sometimes mislead clinicians, who are required to make a decision and choose among all competing treatments. In addition, previous meta-epidemiological studies have reported that some SRs/MAs actually omitted and did not

cite previous review articles even though the research question was identical.[4,8]

Why it is important to do this review

How do we explain these discrepant results between multiple SRs/MAs on the same topic? Some possible explanations for these problems have been suggested, such as the differences of each review's eligibility criteria, the publication of updated versions, inclusion or exclusion of unpublished data, different databases searched, search dates, language restrictions, errors in data extraction, and statistical methods for data synthesis.[2-10] However, it is unclear which factor is the most influential and whether there are other unknown causes. Some recent studies have reported that rapid growth of SRs/MAs regarding antidepressant medications was linked to industry sponsorship.[1,11] In the field of major surgery, as far as the present authors are aware, there has been no meta-epidemiological study that has examined the problem of redundant and overlapping meta-analyses.

Objectives

The primary objectives of this study are 1) to describe how often SRs/MAs of RCTs that were published almost at the same time on the same topic overlaps with one another, and 2) to investigate the cause of discrepant results between multiple SRs/MAs. In addition, we will sequentially assess the quality of these multiple SRs/MAs. The hypothesis of the proposed study is that there are many redundant overlapping publications with conflicting results and various qualities, which represent wasted efforts for investigators and peer reviewers and may

well mislead the clinicians and policymakers in understanding of the results.

METHODS AND ANALYSIS

Study design

A meta-epidemiological study.

Eligibility criteria

We will select the studies according to the following inclusion and exclusion criteria.

Inclusion criteria:

1. SRs/MAs of only RCTs
2. Study populations of RCTs are patients that underwent chest and abdominal surgeries. We define chest surgery as any surgical procedure involving intrathoracic organs (e.g. surgery for coronary artery bypass graft [CABG] and surgery for lung, mediastinal, and pleural diseases). We define abdominal surgery as deliberate breach of peritoneum or retroperitoneum, including gastrointestinal surgery, abdominal aortic surgery, urological surgery, and obstetrics and gynecologic surgery.
3. Interventions (or comparisons) of RCTs are any surgical interventions, that were performed in the operating room (OR). We will include both comparison of surgical versus surgical intervention and comparison of surgical versus non-surgical intervention (e.g., conservative and pharmacological intervention). We will also include interventions regarding wound management and drain management if these were performed in the OR.

4. We will include any outcomes reported by the SRs/MAs, including continuous and dichotomous outcomes.

Exclusion criteria:

1. SRs/MAs that include both RCTs and observational studies
2. SRs/MAs that include both RCTs and quasi-RCTs
3. Network meta-analyses
4. Individual-patient data meta-analyses

Search strategy and study selection

First, we will use the MEDLINE (via PubMed) database to identify recent SRs/MAs of RCTs published in 2015 in the field of major surgical interventions. We will use a combination of Medical Subject Headings (MeSH) terms relevant to systematic reviews and surgery: (systematic[sb] AND ("surgery" [subheading] AND 2015 [dp]) without language restriction. We will exclude studies that do not meet our eligibility criteria based on titles and abstracts, and then read the full text to decide whether papers with potentially relevant titles and abstracts meets our eligibility criteria. Those that meet our eligibility criteria at this point will be termed as the "benchmark" SRs/MAs and topics. We show their eligibility criteria above. If there are more than two same/similar topics in 2015, we will set the broadest one regarding study populations as the "benchmark" topic.

Second, we will perform a manual hand-search to identify similar previous SRs/MAs of

RCTs on the same topics that were published from 2011 through 2015 in MEDLINE. To be more specific, after identifying "benchmark" SRs/MAs published in 2015, we will carry out this manual hand-search to identify the previous overlapping MAs/SRs on the same topic that were published within 5 years of the "benchmark" SRs/MAs from MEDLINE and bibliographies of included articles, according to the titles and abstracts. The key-words and research question provided within the article will be used for the search. Reference lists of review articles and original RCTs will be considered as additional sources of information. SRs/MAs will be selected according to the population, intervention, and comparator only. In other words, we will not place restrictions on outcomes, as long as the SRs/MAs share common study populations, surgical interventions, and comparators. We will not place language restrictions at this stage, either.

Two pairs of two trained researchers will perform the title and abstract review, full-paper screening, and data extraction. Two researchers will independently evaluate if a SR/MA is eligible and if the research question is similar to that of the "benchmark" review. Any disagreements will be resolved through discussions or through involvement of a third researcher.

Data extraction and management

Two researchers will independently read each full-paper and extract data in duplicate using a standardized form to ensure consistency of extracted data for each study. The following

information will be extracted:

1. Journal and study characteristics (lead author's name and country affiliation, official publication year, journal name, and journal impact factor)
2. Search methodology (the name and number of databases searched, date of last search, language restriction, and restrictions on publication status)
3. Research question of SRs/MAs (PICO: participant characteristics, intervention/comparison details, and outcome measures)
4. Characteristics of SRs/MAs (number of eligible RCTs, sample size, effect size, statistical approach [e.g., fixed effects vs. random effects model], citation of previous SRs/MAs and presence or absence of industry funding)

We will resolve any disagreement in consultation with the third investigator of the review team.

Data analysis

Descriptive statistics will be used to summarize characteristics of each of the included SRs/MAs on the same research question. We will tabulate the number of previous SRs/MAs on the same research question that were published within 5 years of publication of the "benchmark" SRs/MAs. Next for each topic, we will describe the differences in number of RCTs included, sample size, effect size, and variability between SRs/MAs. We will compare the coverage ratio of all RCTs that were published until the publication year of each SRs/MAs.

The difference in treatment effect estimates, expressed either as odds ratio (OR) or standardized mean difference (SMD), will be compared between each of the older meta-analyses and the latest meta-analysis. If the original studies used other efficacy indexes and provided sufficient data for the calculations, we will convert them into ORs or SMDs. We will calculate relative odds ratio (ROR) or the difference in SMDs and their 95% confidence intervals (CIs).

We will also assess the difference in quality of each SRs/MAs on the same research question. To evaluate study quality, we will use the "A Measurement Tool to Assess Systematic Reviews" (AMSTAR[12]) instrument. Regarding the AMSTAR score, reported points will be assigned as follows: yes = 1, no = 0, not applicable = 1.[13] The difference in study quality, expressed as AMSTAR scores will be compared between each SRs/MAs.

Finally, we will investigate the potential reasons to explain the discrepant results, if any, between multiple SRs/MAs. We will evaluate which factors influence these differences and whether there are some other unexpected causes.

Statistical analyses will be two-sided, with a P value of 0.05 indicating statistical significance. All analyses will be performed using Stata/SE 11 (StataCorp, College Station, TX, USA).

ETHICS AND DISSEMINATION

This meta-epidemiological study does not require ethical approval. We will publish the findings of this study in a peer-reviewed scientific journal and present them at scientific conferences. The results of this research will be disseminated electronically or in print, as well as among internet communities.

DISCUSSION

Strengths and limitations of study

We have presented the study protocol for a meta-epidemiological investigation with respect to redundant publications of overlapping SRs/MAs on the same topic in major surgery. Our study has several strengths. First, most previous studies were restricted to some specific topics[2,3,6-11]. To our knowledge, this is the first effort to investigate the cause of discrepant results between multiple SRs/MAs on many and unspecified topics all together. Readers of our research can more confidently generalize our findings. Second, unlike most previous studies that evaluated the recent SRs/MAs of pharmacological treatments,[3,4,7,11] our study will examine those of surgical interventions. Thus, our study will provide a more clear assessment of the results by minimizing the impact of industry sponsorship that would be typical of pharmacological treatments. Third, we will employ a well-designed systematic approach, including the use of standardized and pilot-tested screening with a well-trained research team.

There are, however, some limitations to our study. First, judging whether the topic is

identical or different according to the similarity of the research question (and PICO) may be difficult. In order to overcome this problem, we will perform several pilot tests for selecting SRs/MAs and will operationalize a consensus procedure to judge the similarity of the research question in our review team. Second, we will search only MEDLINE/PubMed for SRs/MAs of surgical intervention trials. We might miss some additional relevant SRs/MAs about a given topic. This could potentially indicate that overlapping of SRs/MAs on a single topic is more redundant than we will record. However, limiting the scope of the review to MEDLINE/PubMed will make our study more applicable to the real world use of the SRs/MAs by the clinicians. Third, publication speed may vary across journals: the time lag between manuscript submission (or acceptance) dates and its official publication dates should be considered as an important factor that might affect the coverage ratio of all RCTs that were published until the publication year/month of the SRs/MAs on the certain topic.[14,15] We therefore plan to perform sensitivity analyses, if possible, by using date of the last database search to check for the robustness of the observed findings.

Despite possible methodological limitations, our findings of the proposed research may have important implications for researchers and clinical decision makers. The high variability in results between SRs/MAs on the same topic may indicate a potential risk of the accepted wisdom about the hierarchy of evidence levels.

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Authors' contributions

MK, AK, and TAF contributed to the conception and design of the research. MK, AK, MT, KY, and TAF contributed to the development of the protocol. MK drafted the manuscript. AK and TAF critically reviewed the manuscript for important intellectual content and all authors read and approved the final protocol.

Competing interests

TAF has received lecture fees from Eli Lilly, Janssen, Meiji, MSD, Otsuka, Pfizer and Tanabe-Mitsubishi, and consultancy fees from Takeda Science Foundation. He has received royalties from Igaku-Shoin and Nihon Bunka Kagaku-sha publishers. He has received research support from Mochida and Tanabe-Mitsubishi. The other authors declare no competing interests.

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References

1. Ioannidis JP. The Mass Production of Redundant, Misleading, and Conflicted Systematic Reviews and Meta-analyses. *Milbank Q* 2016;94:485-514.
2. Riaz IB, Khan MS, Riaz H, et al. Disorganized Systematic Reviews and Meta-analyses: Time to Systematize the Conduct and Publication of These Study Overviews? *Am J Med* 2016;129:339.e11-8.
3. Siontis KC, Hernandez-Boussard T, Ioannidis JP. Overlapping meta-analyses on the same topic: survey of published studies. *BMJ* 2013;347:f4501.
4. Helfer B, Prosser A, Samara MT, et al. Recent meta-analyses neglect previous systematic reviews and meta-analyses about the same topic: a systematic examination. *BMC Med* 2015;13:82.
5. Useem J, Brennan A, LaValley M, et al. Systematic Differences between Cochrane and Non-Cochrane Meta-Analyses on the Same Topic: A Matched Pair Analysis. *PLoS One* 2015;10:e0144980.
6. Zhang H, Tang H, He Q, et al. Surgical Versus Conservative Intervention for Acute Achilles Tendon Rupture: A PRISMA-Compliant Systematic Review of Overlapping Meta-Analyses. Medicine (Baltimore). 2015;94:e1951.
7. Créquit P, Trinquart L, Yavchitz A, et al. Wasted research when systematic reviews fail to provide a complete and up-to-date evidence synthesis: the example of lung cancer. *BMC Med* 2016;14:8.

8. Mascarenhas R. Is double-row rotator cuff repair clinically superior to single-row rotator cuff repair: a systematic review of overlapping meta-analyses. *Arthroscopy* 2014;30:1156-65

9. Mascarenhas R. Does Double-Bundle Anterior Cruciate Ligament Reconstruction Improve Postoperative Knee Stability Compared With Single-Bundle Techniques? A Systematic Review of Overlapping Meta-analyses. *Arthroscopy* 2015;31:1185-96

10. Trinquart L, Johns DM, Galea S. Why do we think we know what we know? A metaknowledge analysis of the salt controversy. *Int J Epidemiol* 2016;45:251-60.

11. Ebrahim S, Bance S, Athale A, et al. Meta-analyses with industry involvement are massively published and report no caveats for antidepressants. *J Clin Epidemiol* 2016;70:155-63.

12. Shea BJ, Grimshaw JM, Wells GA, et al. Development of AMSTAR: a measurement tool to assess the methodological quality of systematic reviews. *BMC Med Res Methodol* 2007;7:10.

13. Tunis AS, McInnes MD, Hanna R, et al. Association of study quality with completeness of reporting: have completeness of reporting and quality of systematic reviews and meta-analyses in major radiology journals changed since publication of the PRISMA statement? *Radiology* 2013;269:413-26.

14. Chen H, Chen CH, Jhanji V. Publication times, impact factors, and advance online publication in ophthalmology journals. *Ophthalmology* 2013;120:1697-701.

15. Heneberg P. Effects of print publication lag in dual format journals on scientometric indicators. *PLoS One* 2013;8:e59877.

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	page No	Checklist item
ADMINISTRATIVE INFORMATION		
Title:		
Identification	**p.1**	Identify the report as a protocol of a systematic review
Update	**N/A***	If the protocol is for an update of a previous systematic review, identify as such
Registration	**p.4**	If registered, provide the name of the registry (such as PROSPERO) and registration number
Authors:		
Contact	**p.1,2,14**	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author
Contributions	**p.14**	Describe contributions of protocol authors and identify the guarantor of the review
Amendments	**N/A***	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	**p.14,15**	Indicate sources of financial or other support for the review
Sponsor	**p.14,15**	Provide name for the review funder and/or sponsor
Role of sponsor or funder	**p.14,15**	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol
INTRODUCTION		
Rationale	**p.5,6**	Describe the rationale for the review in the context of what is already known
Objectives	**p.6,7**	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)
METHODS		
Eligibility criteria	**p.7,8**	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
Information sources	**p.8,9**	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
Search strategy	**p.8,9**	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated
Study records:		
Data management	**p.9,10**	Describe the mechanism(s) that will be used to manage records and data throughout the review

Selection process	**p.8-10**	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	**p.8-10**	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	**p.9-11**	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	**p.8**	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale
Risk of bias in individual studies	**N/A***	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
Data synthesis	**p.10,11**	Describe criteria under which study data will be quantitatively synthesised
	p.10,11	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)
	p.13	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression)
	p.10,11	If quantitative synthesis is not appropriate, describe the type of summary planned
Meta-bias(es)	**N/A***	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies)
Confidence in cumulative evidence	**N/A***	Describe how the strength of the body of evidence will be assessed (such as GRADE)

*** 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.

N/A*: These are not applicable TO our manuscript because it is a meta-epidemiological study.

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Introduction:

We are witnessing an explosive increase in redundant and overlapping publications of systematic review and meta-analyses (SRs/MAs) on the same topic, which often present conflicting results and interpretations, in the current medical literature. They represent wasted efforts on the part of investigators and peer reviewers and may confuse and possibly mislead clinicians and policymakers. Here, we present a protocol for a meta-epidemiological investigation to describe how often there are overlapping SRs/MAs on the same topic, to assess the quality of these multiple publications, and to investigate the causes of discrepant results between multiple SRs/MAs in the field of major surgery.

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Objectives

The primary objectives of this study are 1) to describe how often SRs/MAs of RCTs that were published almost at the same time on the same topic overlaps with one another, and 2) to investigate the cause of discrepant results between multiple SRs/MAs. In addition, we will sequentially assess the quality of these multiple SRs/MAs. The hypothesis of the proposed

study is that there are many redundant overlapping publications with conflicting results and various qualities, which represent wasted efforts for investigators and peer reviewers and may well mislead the clinicians and policymakers in understanding of the results.

METHODS AND ANALYSIS

Study design

A meta-epidemiological study.

Eligibility criteria

We will select the studies according to the following inclusion and exclusion criteria.

Inclusion criteria:

1. SRs/MAs of only RCTs
2. Study populations of RCTs are patients that underwent chest and abdominal surgeries. We define chest surgery as any surgical procedure involving intrathoracic organs (e.g. surgery for coronary artery bypass graft [CABG] and surgery for lung, mediastinal, and pleural diseases). We define abdominal surgery as deliberate breach of peritoneum or retroperitoneum, including gastrointestinal surgery, abdominal aortic surgery, urological surgery, and obstetrics and gynecologic surgery.
3. Interventions (or comparisons) of RCTs are any surgical interventions that were abdominal or chest procedures performed in the operating room (OR). We will include both comparisons of surgical versus surgical interventions and comparisons of surgical

versus non-pharmacological interventions.

4. We will include any outcomes reported by the SRs/MAs, including continuous and dichotomous outcomes.

Exclusion criteria:

1. SRs/MAs that include both RCTs and observational studies
2. SRs/MAs that include both RCTs and quasi-RCTs
3. Network meta-analyses
4. Individual-patient data meta-analyses
5. Interventions (or comparisons) of RCTs are any pharmacological interventions

Search strategy and study selection

First, we will use the MEDLINE (via PubMed) database to identify recent SRs/MAs of RCTs published in 2015 in the field of major surgical interventions. We will use a straightforward combination of Medical Subject Headings (MeSH) terms relevant to systematic reviews and surgery: (systematic[sb] AND ("surgery" [subheading] AND 2015 [dp]) without language restriction. We will exclude studies that do not meet our eligibility criteria based on titles and abstracts, and then read the full text to decide whether papers with potentially relevant titles and abstracts meets our eligibility criteria. Those that meet our eligibility criteria at this point will be termed as the "benchmark" SRs/MAs and topics. We show their eligibility criteria above. If there are more than two same/similar topics in 2015,

we will set the broadest one regarding study populations as the "benchmark" topic. For example, when study populations of study A is a subgroup of study B, we will set study B as a "benchmark" SRs/MAs or topics.

Second, we will conduct screening in MEDLINE to identify similar previous SRs/MAs of RCTs on the same topics that were published from 2011 through 2015. To be more specific, after identifying "benchmark" SRs/MAs of RCTs published in 2015, we will carry out this process of screening in MEDLINE to identify the previous overlapping MAs/SRs of RCTs on the same topic that were published within 5 years of the "benchmark" SRs/MAs and bibliographies of included articles, according to the titles and abstracts. The key-words and research question provided within the article will be used for the search. Reference lists of review articles and original RCTs will be considered as additional sources of information. SRs/MAs will be selected according to the population, intervention, and comparator only. In other words, we will not place restrictions on outcomes, as long as the SRs/MAs share common study populations, surgical interventions, and comparators. We will not place language restrictions at this stage, either.

Two pairs of two trained researchers will perform the title and abstract review, full-paper screening, and data extraction. Two researchers will independently evaluate if a SR/MA is eligible and if the research question is similar to that of the "benchmark" review. Any disagreements will be resolved through discussions or through involvement of a third researcher.

Data extraction and management

Two researchers will independently read each full-paper and extract data in duplicate using a standardized form to ensure consistency of extracted data for each study. The following information will be extracted:

1. Journal and study characteristics (lead author's name and country affiliation, official publication year, journal name, and journal impact factor, the presence or absence of methodologist in the list of co-authors)
2. Search methodology (the name and number of databases searched, date of last search, language restriction, and restrictions on publication status)
3. Research question of SRs/MAs (PICO: participant characteristics, intervention/comparison details, and outcome measures)
4. Characteristics of SRs/MAs (number of eligible RCTs, sample size, effect size, statistical approach [e.g., fixed effects vs. random effects model], citation of previous SRs/MAs and the presence or absence of industry funding)

We will resolve any disagreement in consultation with the third investigator of the review team.

Data analysis

Descriptive statistics will be used to summarize characteristics of each of the included

SRs/MAs on the same research question. We will tabulate the number of previous SRs/MAs of RCTs on the same research question that were published within 5 years of publication of the "benchmark" SRs/MAs. Next for each topic, we will describe the differences in number of RCTs included, sample size, effect size, and variability between SRs/MAs. We will compare the coverage ratio of all RCTs that were published until the publication year of each SRs/MAs. The difference in treatment effect estimates, expressed either as odds ratio (OR) or standardized mean difference (SMD), will be compared between each of the older meta-analyses and the latest meta-analysis. If the original studies used other efficacy indexes and provided sufficient data for the calculations, we will convert them into ORs or SMDs. We will calculate relative odds ratio (ROR) or the difference in SMDs and their 95% confidence intervals (CIs), as were done in some previous meta-epidemiological studies[12,13].

We will also assess the difference in quality of each SRs/MAs on the same research question. To evaluate study quality, we will use the "A Measurement Tool to Assess Systematic Reviews" (AMSTAR[14]) instrument. Regarding the AMSTAR score, reported points will be assigned as follows: yes = 1, no = 0, not applicable = 1.[15] The difference in study quality, expressed as AMSTAR scores will be compared between each SRs/MAs.

Finally, we will investigate the potential reasons to explain the discrepant results, if any, between multiple SRs/MAs. We will evaluate which factors (e.g. comprehensiveness of search, number of eligible RCTs, statistical approach and industry funding) influence these differences and whether there are some other unexpected causes. Thus, we might conduct

additional exploratory analyses.

Statistical analyses will be two-sided, with a P value of 0.05 indicating statistical significance. All analyses will be performed using Stata/SE 11 (StataCorp, College Station, TX, USA).

ETHICS AND DISSEMINATION

This meta-epidemiological study does not require ethical approval. We will publish the findings of this study in a peer-reviewed scientific journal and present them at scientific conferences. The results of this research will be disseminated electronically or in print, as well as among internet communities.

DISCUSSION

Strengths and limitations of study

We have presented the study protocol for a meta-epidemiological investigation with respect to redundant publications of overlapping SRs/MAs on the same topic in major surgery. Our study has several strengths. First, most previous studies were restricted to some specific topics[2,3,6-11]. To our knowledge, this is the first effort to investigate the cause of discrepant results between multiple SRs/MAs on many and unspecified topics all together. Readers of our research can more confidently generalize our findings. Second, unlike most previous studies that evaluated the recent SRs/MAs of pharmacological treatments,[3,4,7,11] our study will

examine those of surgical interventions. Thus, our study will provide a more clear assessment of the results by minimizing the impact of industry sponsorship that would be typical of pharmacological treatments. Third, we will employ a well-designed systematic approach, including the use of standardized and pilot-tested screening with a well-trained research team.

There are, however, some limitations to our study. First, judging whether the topic is identical or different according to the similarity of the research question (and PICO) may be difficult. In order to overcome this problem, we will perform several pilot tests for selecting SRs/MAs and will operationalize a consensus procedure to judge the similarity of the research question in our review team. Second, we will search only MEDLINE/PubMed for SRs/MAs of surgical intervention trials. To assess effects of a certain intervention, we would to have a comprehensive dataset of all heretofore conducted RCTs, published or unpublished, and we need to search all possibly relevant databases and beyond. However, the focus of our review is the likely redundancy and contradictions among the systematic reviews in surgery that can be accessed to and therefore used by clinicians and policy makers. We therefore chose the source that is most often used by clinicians worldwide, namely MEDLINE/PubMed. We might therefore be missing some additional relevant SRs/MAs about a given topic. This could potentially indicate that overlapping of SRs/MAs on a single topic is more redundant than we will record. However, limiting the scope of the review to MEDLINE/PubMed will make our study more applicable to the real world use of the SRs/MAs by the clinicians. Third, publication speed may vary across journals: the time lag between manuscript submission (or

acceptance) dates and its official publication dates should be considered as an important factor that might affect the coverage ratio of all RCTs that were published until the publication year/month of the SRs/MAs on the certain topic.[16,17] We therefore plan to perform sensitivity analyses, if possible, by using date of the last database search to check for the robustness of the observed findings. Fourth, the findings from this review would not be directly generalizable to reviews including both RCTs and non-RCTs, which would have greater sources of heterogeneity in their study conclusions.

Despite possible methodological limitations, our findings of the proposed research may have important implications for researchers and clinical decision makers. The high variability in results between SRs/MAs on the same topic may indicate a potential risk of the accepted wisdom about the hierarchy of evidence levels.

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Authors' contributions

MK, AK, and TAF contributed to the conception and design of the research. MK, AK, MT, KY, and TAF contributed to the development of the protocol. MK drafted the manuscript. AK and TAF critically reviewed the manuscript for important intellectual content and all authors read and approved the final protocol.

Competing interests

TAF has received lecture fees from Eli Lilly, Janssen, Meiji, MSD, Otsuka, Pfizer and Tanabe-Mitsubishi, and consultancy fees from Takeda Science Foundation. He has received royalties from Igaku-Shoin and Nihon Bunka Kagaku-sha publishers. He has received research support from Mochida and Tanabe-Mitsubishi. The other authors declare no competing interests.

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References

1. Ioannidis JP. The Mass Production of Redundant, Misleading, and Conflicted Systematic Reviews and Meta-analyses. *Milbank Q* 2016;94:485-514.
2. Riaz IB, Khan MS, Riaz H, et al. Disorganized Systematic Reviews and Meta-analyses: Time to Systematize the Conduct and Publication of These Study Overviews? *Am J Med* 2016;129:339.e11-8.
3. Siontis KC, Hernandez-Boussard T, Ioannidis JP. Overlapping meta-analyses on the same topic: survey of published studies. *BMJ* 2013;347:f4501.
4. Helfer B, Prosser A, Samara MT, et al. Recent meta-analyses neglect previous systematic reviews and meta-analyses about the same topic: a systematic examination. *BMC Med* 2015;13:82.
5. Useem J, Brennan A, LaValley M, et al. Systematic Differences between Cochrane and Non-Cochrane Meta-Analyses on the Same Topic: A Matched Pair Analysis. *PLoS One* 2015;10:e0144980.
6. Zhang H, Tang H, He Q, et al. Surgical Versus Conservative Intervention for Acute Achilles Tendon Rupture: A PRISMA-Compliant Systematic Review of Overlapping

Meta-Analyses. Medicine (Baltimore). 2015;94:e1951.

7. Créquit P, Trinquart L, Yavchitz A, et al. Wasted research when systematic reviews fail to provide a complete and up-to-date evidence synthesis: the example of lung cancer. *BMC Med* 2016;14:8.

8. Mascarenhas R. Is double-row rotator cuff repair clinically superior to single-row rotator cuff repair: a systematic review of overlapping meta-analyses. *Arthroscopy* 2014;30:1156-65

9. Mascarenhas R. Does Double-Bundle Anterior Cruciate Ligament Reconstruction Improve Postoperative Knee Stability Compared With Single-Bundle Techniques? A Systematic Review of Overlapping Meta-analyses. *Arthroscopy* 2015;31:1185-96

10. Trinquart L, Johns DM, Galea S. Why do we think we know what we know? A metaknowledge analysis of the salt controversy. *Int J Epidemiol* 2016;45:251-60.

11. Ebrahim S, Bance S, Athale A, et al. Meta-analyses with industry involvement are massively published and report no caveats for antidepressants. *J Clin Epidemiol* 2016;70:155-63.

12. Hrobjartsson A, Thomsen AS, Emanuelsson F, et al. Observer bias in randomised clinical trials with binary outcomes: systematic review of trials with both blinded and non-blinded outcome assessors. *BMJ* 2012;344:e1119.

13. Hemkens LG, Contopoulos-Ioannidis DG, Ioannidis JP. Agreement of treatment effects for mortality from routinely collected data and subsequent randomized trials:

meta-epidemiological survey. *BMJ* 2016;352:i493.

14. Shea BJ, Grimshaw JM, Wells GA, et al. Development of AMSTAR: a measurement tool to assess the methodological quality of systematic reviews. *BMC Med Res Methodol* 2007;7:10.

15. Tunis AS, McInnes MD, Hanna R, et al. Association of study quality with completeness of reporting: have completeness of reporting and quality of systematic reviews and meta-analyses in major radiology journals changed since publication of the PRISMA statement? *Radiology* 2013;269:413-26.

16. Chen H, Chen CH, Jhanji V. Publication times, impact factors, and advance online publication in ophthalmology journals. *Ophthalmology* 2013;120:1697-701.

17. Heneberg P. Effects of print publication lag in dual format journals on scientometric indicators. *PLoS One* 2013;8:e59877.

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	page No	Checklist item
ADMINISTRATIVE INFORMATION		
Title:		
Identification	**p.1**	Identify the report as a protocol of a systematic review
Update	**N/A***	If the protocol is for an update of a previous systematic review, identify as such
Registration	**p.4**	If registered, provide the name of the registry (such as PROSPERO) and registration number
Authors:		
Contact	**p.1,2,14**	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author
Contributions	**p.14**	Describe contributions of protocol authors and identify the guarantor of the review
Amendments	**N/A***	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	**p.14,15**	Indicate sources of financial or other support for the review
Sponsor	**p.14,15**	Provide name for the review funder and/or sponsor
Role of sponsor or funder	**p.14,15**	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol
INTRODUCTION		
Rationale	**p.5,6**	Describe the rationale for the review in the context of what is already known
Objectives	**p.6,7**	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)
METHODS		
Eligibility criteria	**p.7,8**	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
Information sources	**p.8,9**	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
Search strategy	**p.8,9**	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated
Study records:		
Data management	**p.9,10**	Describe the mechanism(s) that will be used to manage records and data throughout the review

Selection process	**p.8-10**	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	**p.8-10**	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	**p.9-11**	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	**p.8**	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale
Risk of bias in individual studies	**N/A***	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
Data synthesis	**p.10,11**	Describe criteria under which study data will be quantitatively synthesised
	p.10,11	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)
	p.13	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression)
	p.10,11	If quantitative synthesis is not appropriate, describe the type of summary planned
Meta-bias(es)	**N/A***	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies)
Confidence in cumulative evidence	**N/A***	Describe how the strength of the body of evidence will be assessed (such as GRADE)

*** 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.

N/A*: These are not applicable TO our manuscript because it is a meta-epidemiological study.

BMJ Open

Redundant systematic reviews on the same topic in surgery: a study protocol for a meta-epidemiological investigation

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Primary Subject Heading:	Epidemiology
Secondary Subject Heading:	Surgery
Keywords:	meta-analysis, systematic review, same topic, overlapping, meta-epidemiology, surgical intervention

Study protocol

Title:

Redundant systematic reviews on the same topic in surgery: a study protocol for a meta-epidemiological investigation

Author:

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ABSTRACT

Introduction:

We are witnessing an explosive increase in redundant and overlapping publications of systematic review and meta-analyses (SRs/MAs) on the same topic, which often present conflicting results and interpretations, in the current medical literature. They represent wasted efforts on the part of investigators and peer reviewers and may confuse and possibly mislead clinicians and policymakers. Here, we present a protocol for a meta-epidemiological investigation to describe how often there are overlapping SRs/MAs on the same topic, to assess the quality of these multiple publications, and to investigate the causes of discrepant results between multiple SRs/MAs in the field of major surgery.

Methods and analysis:

We will use MEDLINE/PubMed to identify all SRs/MAs of randomized controlled trials (RCTs) published in 2015 regarding major surgical interventions. After identifying the "benchmark" SRs/MAs published in 2015, a process of screening in MEDLINE will be carried out to identify the previous SRs/MAs of RCTs on the same topic that were published within 5 years of the "benchmark" SRs/MAs. We will tabulate the number of previous SRs/MAs on the same topic of RCTs, and then describe their variations in numbers of RCTs included, sample sizes, effect size estimates and other characteristics. We will also assess the differences in quality of each SRs/MAs using the AMSTAR score. Finally, we will investigate the potential reasons to explain the discrepant results between multiple SRs/MAs.

Ethics and dissemination:

No formal ethical approval and informed consent are required because this study will not collect primary individual data. The intended audiences of the findings include clinicians, healthcare researchers, and policymakers. We will publish our findings as a scientific report in a peer-reviewed journal.

Trial registration number:

In PROSPERO CRD42017059077, March 2017

Strengths and limitations of this study

- This meta-epidemiological study is the first to focus on the cause of discrepant results between multiple overlapping SRs/MAs on many and unspecified topics in surgery.
- Our study will provide a more clear assessment of the results by minimizing the impact of industry sponsorship that would be typical of pharmacological interventions, because our study will mainly examine those of surgical interventions.
- Judging whether the topic is identical or different according to the similarity of the research question may be difficult.
- The time lag between manuscript submission dates and its official publication dates should be considered as an important factor that might affect the proportion of all available RCTs that are included in a particular SR/MA.
- We will perform the article search using a single database (MEDLINE via PubMed) to

identify SRs/MAs.

INTRODUCTION

Description of the condition

In recent years, the number of published systematic reviews (SRs) and meta-analyses (MAs) have been increasing explosively in many medical fields.[1-4] When a small number of randomized control trials (RCTs) of new research questions are published, new SRs/MAs soon follow these RCTs. Indeed, it is becoming more and more difficult to find a new research question that nobody has examined as a systematic review article in medical journals. Furthermore, many topics addressed by SRs/MAs often overlap with each other entirely or partially, and instances have been reported where more than 10 SRs/MAs were published on a single topic in a limited span of time.[2-3] These potentially redundant publications may represent duplicated efforts for researchers, peer reviewers, and editors of the medical journals.

The picture is even more confusing and distressing for readers of the medical literature. Some previous studies have shown that the numbers of pooled RCTs and included patient' sample sizes are quite different across SRs/MAs on the same topic.[2,3,5-10] It is then a natural consequence that there are discrepancies between results of SRs/MAs; different effect sizes, with different statistical precision, and even different directions of effect have been reported.[2,3,5-10] Such conflicting results can confuse and sometimes mislead clinicians, who are

required to make a decision and choose among all competing treatments. In addition, previous meta-epidemiological studies have reported that some SRs/MAs actually omitted and did not cite previous review articles even though the research question was identical. [4,8]

Why it is important to do this review

How do we explain these discrepant results between multiple SRs/MAs on the same topic? Some possible explanations for these problems have been suggested, such as the differences of each review's eligibility criteria, the publication of updated versions, inclusion or exclusion of unpublished data, different databases searched, search dates, language restrictions, errors in data extraction, and statistical methods for data synthesis.[2-10] However, it is unclear which factor is the most influential and whether there are other unknown causes. Some recent studies have reported that rapid growth of SRs/MAs regarding antidepressant medications was linked to industry sponsorship.[1,11] In the field of major surgery, as far as the present authors are aware, there has been no meta-epidemiological study that has examined the problem of redundant and overlapping meta-analyses.

Objectives

The primary objectives of this study are 1) to describe how often SRs/MAs of RCTs that were published almost at the same time on the same topic overlaps with one another, and 2) to investigate the cause of discrepant results between multiple SRs/MAs. In addition, we will sequentially assess the quality of these multiple SRs/MAs. The hypothesis of the proposed

study is that there are many redundant overlapping publications with conflicting results and various qualities, which represent wasted efforts for investigators and peer reviewers and may well mislead the clinicians and policymakers in understanding of the results.

METHODS AND ANALYSIS

Study design

A meta-epidemiological study.

Eligibility criteria

We will select the studies according to the following inclusion and exclusion criteria.

Inclusion criteria:

1. SRs/MAs of only RCTs
2. Study populations of RCTs are patients that underwent chest and abdominal surgeries. We define chest surgery as any surgical procedure involving intrathoracic organs (e.g. surgery for coronary artery bypass graft [CABG] and surgery for lung, mediastinal, and pleural diseases). We define abdominal surgery as deliberate breach of peritoneum or retroperitoneum, including gastrointestinal surgery, abdominal aortic surgery, urological surgery, and obstetrics and gynecologic surgery.
3. Interventions (or comparisons) of RCTs are any surgical interventions that were abdominal or chest procedures performed in the operating room (OR). We will include both comparisons of surgical versus surgical interventions and comparisons of surgical

versus non-pharmacological interventions.

4. We will include any outcomes reported by the SRs/MAs, including continuous and dichotomous outcomes.

Exclusion criteria:

1. SRs/MAs that include both RCTs and observational studies
2. SRs/MAs that include both RCTs and quasi-RCTs
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Search strategy and study selection

First, we will use the MEDLINE (via PubMed) database to identify recent SRs/MAs of RCTs published in 2015 in the field of major surgical interventions. We will use a straightforward combination of Medical Subject Headings (MeSH) terms relevant to systematic reviews and surgery: (systematic[sb] AND ("surgery" [subheading] AND 2015 [dp]) without language restriction. We will exclude studies that do not meet our eligibility criteria based on titles and abstracts, and then read the full text to decide whether papers with potentially relevant titles and abstracts meets our eligibility criteria. Those that meet our eligibility criteria at this point will be termed as the "benchmark" SRs/MAs and topics. We show their eligibility criteria above. If there are more than two same/similar topics in 2015,

we will set the broadest one regarding study populations as the "benchmark" topic. For example, when study populations of study A is a subgroup of study B, we will set study B as a "benchmark" SRs/MAs or topics.

Second, we will conduct screening in MEDLINE to identify similar previous SRs/MAs of RCTs on the same topics that were published from 2011 through 2015. To be more specific, after identifying "benchmark" SRs/MAs of RCTs published in 2015, we will carry out this process of screening in MEDLINE to identify the previous overlapping MAs/SRs of RCTs on the same topic that were published within 5 years of the "benchmark" SRs/MAs and bibliographies of included articles, according to the titles and abstracts. The reviews identified during the bench marking process will be used to identify relevant keywords and then index terms to devise a complete PubMed/Medline search strategy to locate relevant SRs/MAs published between 2011-2015. Reference lists of review articles and original RCTs will be considered as additional sources of information. SRs/MAs will be selected according to the population, intervention, and comparator only. In other words, we will not place restrictions on outcomes, as long as the SRs/MAs share common study populations, surgical interventions, and comparators. We will not place language restrictions at this stage, either.

Two pairs of two trained researchers will perform the title and abstract review, full-paper screening, and data extraction. Two researchers will independently evaluate if a SR/MA is eligible and if the research question is similar to that of the "benchmark" review. Any disagreements will be resolved through discussions or through involvement of a third

researcher.

Data extraction and management

Two researchers will independently read each full-paper and extract data in duplicate using a standardized form to ensure consistency of extracted data for each study. The following information will be extracted:

1. Journal and study characteristics (lead author's name and country affiliation, official publication year, journal name, and journal impact factor, the presence or absence of methodologist in the list of co-authors)
2. Search methodology (the name and number of databases searched, date of last search, language restriction, and restrictions on publication status)
3. Research question of SRs/MAs (PICO: participant characteristics, intervention/comparison details, and outcome measures)
4. Characteristics of SRs/MAs (number of eligible RCTs, sample size, effect size, statistical approach [e.g., fixed effects vs. random effects model], citation of previous SRs/MAs and the presence or absence of industry funding)

We will resolve any disagreement in consultation with the third investigator of the review team.

Data analysis

Descriptive statistics will be used to summarize characteristics of each of the included SRs/MAs on the same research question. We will tabulate the number of previous SRs/MAs of RCTs on the same research question that were published within 5 years of publication of the "benchmark" SRs/MAs. Next for each topic, we will describe the differences in number of RCTs included, sample size, effect size, and variability between SRs/MAs. We will compare the coverage ratio of all RCTs that were published until the publication year of each SRs/MAs. The difference in treatment effect estimates, expressed either as odds ratio (OR) or standardized mean difference (SMD), will be compared between each of the older meta-analyses and the latest meta-analysis. If the original studies used other efficacy indexes and provided sufficient data for the calculations, we will convert them into ORs or SMDs. We will calculate relative odds ratio (ROR) or the difference in SMDs and their 95% confidence intervals (CIs), as were done in some previous meta-epidemiological studies[12,13].

We will also assess the difference in quality of each SRs/MAs on the same research question. To evaluate study quality, we will use the "A Measurement Tool to Assess Systematic Reviews" (AMSTAR[14]) instrument. Regarding the AMSTAR score, reported points will be assigned as follows: yes = 1, no = 0, not applicable = 1.[15] The difference in study quality, expressed as AMSTAR scores will be compared between each SRs/MAs.

Finally, we will investigate the potential reasons to explain the discrepant results, if any, between multiple SRs/MAs. We will evaluate which factors (e.g. comprehensiveness of search, number of eligible RCTs, statistical approach and industry funding) influence these

differences and whether there are some other unexpected causes. Thus, we might conduct additional exploratory analyses.

Statistical analyses will be two-sided, with a P value of 0.05 indicating statistical significance. All analyses will be performed using Stata/SE 11 (StataCorp, College Station, TX, USA).

ETHICS AND DISSEMINATION

This meta-epidemiological study does not require ethical approval. We will publish the findings of this study in a peer-reviewed scientific journal and present them at scientific conferences. The results of this research will be disseminated electronically or in print, as well as among internet communities.

DISCUSSION

Strengths and limitations of study

We have presented the study protocol for a meta-epidemiological investigation with respect to redundant publications of overlapping SRs/MAs on the same topic in major surgery. Our study has several strengths. First, most previous studies were restricted to some specific topics[2,3,6-11]. To our knowledge, this is the first effort to investigate the cause of discrepant results between multiple SRs/MAs on many and unspecified topics all together. Readers of our research can more confidently generalize our findings. Second, unlike most previous

studies that evaluated the recent SRs/MAs of pharmacological treatments,[3,4,7,11] our study will examine those of surgical interventions. Thus, our study will provide a more clear assessment of the results by minimizing the impact of industry sponsorship that would be typical of pharmacological treatments. Third, we will employ a well-designed systematic approach, including the use of standardized and pilot-tested screening with a well-trained research team.

There are, however, some limitations to our study. First, judging whether the topic is identical or different according to the similarity of the research question (and PICO) may be difficult. In order to overcome this problem, we will perform several pilot tests for selecting SRs/MAs and will operationalize a consensus procedure to judge the similarity of the research question in our review team. Second, we will search only MEDLINE/PubMed for SRs/MAs of surgical intervention trials. To assess effects of a certain intervention, we would to have a comprehensive dataset of all heretofore conducted RCTs, published or unpublished, and we need to search all possibly relevant databases and beyond. However, the focus of our review is the likely redundancy and contradictions among the systematic reviews in surgery that can be accessed to and therefore used by clinicians and policy makers. We therefore chose the source that is most often used by clinicians worldwide, namely MEDLINE/PubMed. We might therefore be missing some additional relevant SRs/MAs about a given topic. This could potentially indicate that overlapping of SRs/MAs on a single topic is more redundant than we will record. However, limiting the scope of the review to MEDLINE/PubMed will make our study more applicable to the real world use of the SRs/MAs by the clinicians. Third,

publication speed may vary across journals: the time lag between manuscript submission (or acceptance) dates and its official publication dates should be considered as an important factor that might affect the coverage ratio of all RCTs that were published until the publication year/month of the SRs/MAs on the certain topic.[16,17] We therefore plan to perform sensitivity analyses, if possible, by using date of the last database search to check for the robustness of the observed findings. Fourth, the findings from this review would not be directly generalizable to reviews including both RCTs and non-RCTs, which would have greater sources of heterogeneity in their study conclusions.

Despite possible methodological limitations, our findings of the proposed research may have important implications for researchers and clinical decision makers. The high variability in results between SRs/MAs on the same topic may indicate a potential risk of the accepted wisdom about the hierarchy of evidence levels.

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Authors' contributions

MK, AK, and TAF contributed to the conception and design of the research. MK, AK, MT, KY, and TAF contributed to the development of the protocol. MK drafted the manuscript. AK and TAF critically reviewed the manuscript for important intellectual content and all authors read and approved the final protocol.

Competing interests

TAF has received lecture fees from Eli Lilly, Janssen, Meiji, MSD, Otsuka, Pfizer and Tanabe-Mitsubishi, and consultancy fees from Takeda Science Foundation. He has received royalties from Igaku-Shoin and Nihon Bunka Kagaku-sha publishers. He has received research support from Mochida and Tanabe-Mitsubishi. The other authors declare no competing interests.

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References

1. Ioannidis JP. The Mass Production of Redundant, Misleading, and Conflicted Systematic Reviews and Meta-analyses. *Milbank Q* 2016;94:485-514.
2. Riaz IB, Khan MS, Riaz H, et al. Disorganized Systematic Reviews and Meta-analyses: Time to Systematize the Conduct and Publication of These Study Overviews? *Am J Med* 2016;129:339.e11-8.
3. Siontis KC, Hernandez-Boussard T, Ioannidis JP. Overlapping meta-analyses on the same topic: survey of published studies. *BMJ* 2013;347:f4501.
4. Helfer B, Prosser A, Samara MT, et al. Recent meta-analyses neglect previous systematic reviews and meta-analyses about the same topic: a systematic examination. *BMC Med* 2015;13:82.
5. Useem J, Brennan A, LaValley M, et al. Systematic Differences between Cochrane and Non-Cochrane Meta-Analyses on the Same Topic: A Matched Pair Analysis. *PLoS One* 2015;10:e0144980.
6. Zhang H, Tang H, He Q, et al. Surgical Versus Conservative Intervention for Acute

Achilles Tendon Rupture: A PRISMA-Compliant Systematic Review of Overlapping Meta-Analyses. Medicine (Baltimore). 2015;94:e1951.

7. Créquit P, Trinquart L, Yavchitz A, et al. Wasted research when systematic reviews fail to provide a complete and up-to-date evidence synthesis: the example of lung cancer. *BMC Med* 2016;14:8.
8. Mascarenhas R. Is double-row rotator cuff repair clinically superior to single-row rotator cuff repair: a systematic review of overlapping meta-analyses. *Arthroscopy* 2014;30:1156-65
9. Mascarenhas R. Does Double-Bundle Anterior Cruciate Ligament Reconstruction Improve Postoperative Knee Stability Compared With Single-Bundle Techniques? A Systematic Review of Overlapping Meta-analyses. *Arthroscopy* 2015;31:1185-96
10. Trinquart L, Johns DM, Galea S. Why do we think we know what we know? A metaknowledge analysis of the salt controversy. *Int J Epidemiol* 2016;45:251-60.
11. Ebrahim S, Bance S, Athale A, et al. Meta-analyses with industry involvement are massively published and report no caveats for antidepressants. *J Clin Epidemiol* 2016;70:155-63.
12. Hrobjartsson A, Thomsen AS, Emanuelsson F, et al. Observer bias in randomised clinical trials with binary outcomes: systematic review of trials with both blinded and non-blinded outcome assessors. *BMJ* 2012;344:e1119.
13. Hemkens LG, Contopoulos-Ioannidis DG, Ioannidis JP. Agreement of treatment effects

for mortality from routinely collected data and subsequent randomized trials: meta-epidemiological survey. *BMJ* 2016;352:i493.

14. Shea BJ, Grimshaw JM, Wells GA, et al. Development of AMSTAR: a measurement tool to assess the methodological quality of systematic reviews. *BMC Med Res Methodol* 2007;7:10.
15. Tunis AS, McInnes MD, Hanna R, et al. Association of study quality with completeness of reporting: have completeness of reporting and quality of systematic reviews and meta-analyses in major radiology journals changed since publication of the PRISMA statement? *Radiology* 2013;269:413-26.
16. Chen H, Chen CH, Jhanji V. Publication times, impact factors, and advance online publication in ophthalmology journals. *Ophthalmology* 2013;120:1697-701.
17. Heneberg P. Effects of print publication lag in dual format journals on scientometric indicators. *PLoS One* 2013;8:e59877.

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	page No	Checklist item
ADMINISTRATIVE INFORMATION		
Title:		
Identification	**p.1**	Identify the report as a protocol of a systematic review
Update	**N/A***	If the protocol is for an update of a previous systematic review, identify as such
Registration	**p.4**	If registered, provide the name of the registry (such as PROSPERO) and registration number
Authors:		
Contact	**p.1,2,14**	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author
Contributions	**p.14**	Describe contributions of protocol authors and identify the guarantor of the review
Amendments	**N/A***	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	**p.14,15**	Indicate sources of financial or other support for the review
Sponsor	**p.14,15**	Provide name for the review funder and/or sponsor
Role of sponsor or funder	**p.14,15**	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol
INTRODUCTION		
Rationale	**p.5,6**	Describe the rationale for the review in the context of what is already known
Objectives	**p.6,7**	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)
METHODS		
Eligibility criteria	**p.7,8**	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
Information sources	**p.8,9**	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
Search strategy	**p.8,9**	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated
Study records:		
Data management	**p.9,10**	Describe the mechanism(s) that will be used to manage records and data throughout the review

Selection process	**p.8-10**	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	**p.8-10**	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	**p.9-11**	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	**p.8**	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale
Risk of bias in individual studies	**N/A***	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
Data synthesis	**p.10,11**	Describe criteria under which study data will be quantitatively synthesised
	p.10,11	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)
	p.13	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression)
	p.10,11	If quantitative synthesis is not appropriate, describe the type of summary planned
Meta-bias(es)	**N/A***	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies)
Confidence in cumulative evidence	**N/A***	Describe how the strength of the body of evidence will be assessed (such as GRADE)

*** 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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N/A*: These are not applicable TO our manuscript because it is a meta-epidemiological study.