BMJ Open

# Association between statistical significance and publication status and time to publication among systematic reviews: a study protocol for a meta-epidemiological investigation



| | |
|---|---|
| Journal: | *BMJ Open* |
| Manuscript ID | bmjopen-2017-018856 |
| Article Type: | Protocol |
| Date Submitted by the Author: | 25-Jul-2017 |
| Complete List of Authors: | Tsujimoto, Yasushi ; School of Public Health in the Graduate School of Medicine, Kyoto University, Department of Healthcare Epidemiology; Kyoritsu Hospital, Department of Nephrology and Dialysis<br>Tsutsumi, Yusuke; School of Public Health in the Graduate School of Medicine, Kyoto University, Department of Healthcare Epidemiology<br>Kataoka, Yuki; School of Public Health in the Graduate School of Medicine, Kyoto University, Department of Healthcare Epidemiology<br>Tsujimoto, Hiraku; Hyogo Prefectural Amagasaki General Medical Center, Hospital Care Research Unit<br>Yamamoto, Yosuke; School of Public Health in the Graduate School of Medicine, Kyoto University, Department of Healthcare Epidemiology<br>Papola, Davide; University of Verona, WHO Collaborating Centre for Research and Training in Mental Health and Service Evaluation; Department of Neuroscience, Biomedicine and Movement Sciences; Section of Psychiatry<br>Guyatt, Gordon; Mcmaster University, Department of Health Research Methods, Evidence and Impact<br>Fukuhara, Shunichi; School of Public Health in the Graduate School of Medicine, Kyoto University, Department of Healthcare Epidemiology<br>Furukawa, Toshi; School of Public Health in the Graduate School of Medicine, Kyoto University, Department of Health Promotion and Human Behavior |
| Primary Subject Heading: | Epidemiology |
| Secondary Subject Heading: | Medical publishing and peer review |
| Keywords: | publication bias, time lag bias, systematic reviews, protocol registration, meta-epidemiological study |
| | |

**Title page**

**Title**

Association between statistical significance and publication status and time to publication among systematic reviews: a study protocol for a meta-epidemiological investigation

**Authors:**

Yasushi Tsujimoto[1,2], Yusuke Tsutsumi[1], Yuki Kataoka[1], Hiraku Tsujimoto[3], Yosuke Yamamoto[1], Davide Papola[4], Gordon H Guyatt[5], Shunichi Fukuhara[1], Toshi A Furukawa[6]

**Affiliations:**

1. Department of Healthcare Epidemiology, School of Public Health in the Graduate School of Medicine, Kyoto University, Yoshida Konoe-cho, Sakyo-ku, Kyoto 606-8501, Japan
2. Department of Nephrology and Dialysis, Kyoritsu Hospital, 16-5 Chuo-cho, Kawanishi, Hyogo 666-0016, Japan
3. Hospital Care Research Unit, Hyogo Prefectural Amagasaki General Medical Center, 2-17-77 Higashi-Naniwa-Cho, Amagasaki, Hyogo 660-8550, Japan
4. WHO Collaborating Centre for Research and Training in Mental Health and Service Evaluation; Department of Neuroscience, Biomedicine and Movement Sciences; Section of Psychiatry, University of Verona, Verona, Italy
5. Department of Health Research Methods, Evidence and Impact, McMaster University, Hamilton, ON L8S 4K1, Canada.
6. Department of Health Promotion and Human Behavior, School of Public Health in

the Graduate School of Medicine, Kyoto University, Yoshida Konoe-cho, Sakyo-ku, Kyoto 606-8501, Japan

**Corresponding author:**

Toshi A Furukawa

Department of Health Promotion and Human Behavior, School of Public Health in the Graduate School of Medicine, Kyoto University, Yoshida Konoe-cho, Sakyo-ku, Kyoto 606-8501, Japan

Phone: +81-75-753-9491

Fax: +81-75-753-4641

Email: furukawa@kuhp.kyoto-u.ac.jp

**Word count: 2404**

**Abstract**

## Introduction

Many studies have indicated the impact of bias in dissemination and publication in medical research. Existence of such bias among clinical trials has been repeatedly pointed out, but it has not been well studied in the field of systematic reviews (SRs). We therefore aim to investigate whether or not publication bias and time lag bias in SRs based on statistical significance in results exist. In addition, we will examine at what stage of paper publication process such bias, if any, creeps in.

## Method and analysis

The present study is a meta-epidemiological study. We will include all SRs of interventions registered in the international prospective register of systematic reviews (PROSPERO) before Dec 2014 if the SR has completed its analysis irrespective of its publication status. All contact authors of eligible SRs will be asked to participate in a survey administered through the Internet. Our primary outcomes are (i) proportion of SRs published as a journal article and (ii) time from protocol registration to full publication of SR as a journal article, defined as time from the registration date to the acceptance date among all the relevant SRs. We will examine the impact of statistically significant findings on the primary outcomes through logistic regression and time to event analyses.

## Ethics and dissemination

Ethics approval will be obtained from the Ethical Committee of the Kyoto University Graduate School of Medicine. This protocol has been registered in the University hospital Medical Information Network (UMIN) Clinical Trials Registry. We will publish our findings in a peer-reviewed journal and also may present them at conferences.

**Trial registration number: UMIN000028325**

**Strengths and limitations of this study**

- This is the first study to contact the authors of unpublished systematic reviews (SRs) and investigate the existence and the magnitude of publication bias and time lag bias in the realm of SRs.
- The factors associated with publication or time to publication of SRs will inform potential preventive measures for these biases
- The generalizability will be limited because the analyses investigating the biases include only those who registered the protocol in the PROSPERO and respond to our survey
- The time to publication may not reflect true time lag bias that is the period between the initiation of the SR and its publication because protocols may be registered after their analyses

## INTRODUCTION

Many studies have reported bias in dissemination and publication of research findings in medicine [1-5]. Bias in dissemination and publication can be introduced at all stages of the publication process after study commencement, such as conducting research and writing up of manuscripts by investigators, and acceptance by journal editors or peer-reviewers.

Publication bias occurs when the choice of authors' write-up and submission or editors' acceptance for publication is influenced by the direction or strength of the study findings [6]. When this happens, findings of published studies will be systematically different from those of unpublished studies and hence from the underlying truth (Figure 1) [7].

Time lag bias is one aspect of publication bias which arises when the speed of publication depends on the direction and nature of the randomized clinical trial (RCT) results [2, 7, 8]. In RCTs, trials without statistical significant results take a longer time before publication than trials with statistical significant results (Figure 1) [4]. One recent study found that the main barrier for publication was at the stage of authors rather than editors or reviewers [7, 9]. With respect to time lag in particular, one can characterize the phenomenon as either delay due to non-significant results, or expedited submission and publication due to significant results.

Bias in dissemination and publication among clinical trials has been well studied, however it has not been much studied in SRs [10]. A survey among first or corresponding authors of SRs indicated that unpublished SRs exist [11]. The authors reported common reasons for not publishing SRs including lack of time and the manuscript being rejected by journals. Statistical significance was not reported as being a major barrier or reason for not publishing, but 65% of respondents reported significant results as a significant

facilitator for publishing SRs – in other words authors are more likely, faced with other pressures, to take the time to complete and submit their review when they have positive results to report. Other studies suggested that statistical significant results were not associated with time to publication of Cochrane reviews [12]. On the other hand, non-Cochrane SRs were likely to report statistical significance findings and positive conclusions [13]. We recently reported more than 30% of non-Cochrane SRs registered in the international prospective register of systematic reviews (PROSPERO) were not published after at least 65 months of registration [14]. These results indicate that publication bias and time lag bias among non-Cochrane SRs may well exist.

This study therefore aims to investigate whether or not publication bias and time lag bias in SRs based on statistical significance exist. We will also evaluate other factors associated with time to publication.

## OBJECTIVES

We aim to evaluate the association between statistical significance and other factors of possible influence and publication status using a number of criteria (full publication in a journal article, submission to any journals, presentation of an abstract at a meeting).

## METHODS AND ANALYSIS

Inclusion and exclusion criteria

All SR protocols of interventions registered in the PROSPERO by 31st Dec 2014 will be eligible. We have chosen this time limit because we expect that it may often take 3 years to complete and publish SR after its registration [14] . We will exclude SRs whose analysis has not been completed and SRs without quantitative synthesis. We will exclude

Cochrane protocols and reviews because their publication process is different from general peer-reviewed journals. We will also exclude SRs of diagnostic test accuracy and prognosis, and SRs with network meta-analysis, individual patient data meta-analyses because different factors are likely to be at play. Figure 2 shows the expected flow diagram of this study.

Search method

We will search the relevant SRs in the PROSPERO. We will use search filters of "Exclude Cochrane protocols" for type of protocol and "Intervention, Prevention or Service Delivery" for type and method of the review. For protocols with "Ongoing and Completed" stage of review, we will search MEDLINE via PubMed to find a full publication, using the authors' names and the keywords for participants or intervention in the PROSPERO because our pilot search indicated the status of the PROSPERO may often not be updated promptly to reflect the true status. For protocols with "Abandoned" stage of review, we will exclude them when their data analyses have not been completed.

Study selection

Four authors (YTsuj, YTsut, HT, and YK) will independently assess the eligibility based on a random sample of 500 of the PROSPERO records identified by the initial search. We will resolve disagreements by discussion between the authors, with another author (TAF) acting as an arbiter.

Data extraction

All records of included SRs will be downloaded from the PROSPERO. Four authors will independently extract the following data from the relevant SRs in the PROSPERO:

Registration and anticipated date of completion, the number of authors, funding sources, conflicts of interests (COIs), stage of review, year of registration, and countries that the study has been conducted. We will define the primary review question of the SR in terms of participant, intervention, comparator, and primary outcome. As the review may provide several comparisons for the same class of interventions and comparators, we will define the primary comparison as the intervention and comparator that are described as the primary or the first one in the intervention and comparator section in the PROSPERO record, and the primary outcomes as all outcomes listed in the primary outcome section of PROSPERO. Should the primary outcome be missing in the primary outcome section of PROSPERO, we will define the one mentioned first as the primary outcome. For SRs published in a journal article, we will extract the date of acceptance. If acceptance date is not available, we will use the publication date for SRs published in open access journals, and contact the authors or the editorial office for SRs published in other journals.

Survey

For eligible SRs, we will contact the authors of the SRs and will ask them to respond to a survey through the Internet. Through the survey, all contact authors of eligible unpublished SRs will be asked whether or not the SR analysis has been completed. Additionally, all contact authors of published or completed but not published SRs will be asked the following information; whether or not each of the primary outcomes in the primary comparison (as defined by a decision rule described in Data extraction section above) was statistically significant; the review team's involvement in any of the trials included in the SR; the author's experience to publish an SR as a lead author before the

PROPERO registration; relationship with a private for-profit consulting firm for SRs; and main barriers to publish the SR according to a classification used in a previous study [11]. In addition, we will ask if someone has published a review addressing the same question. If the authors have completed the analysis but not published it, the following information will be sought; the number of included trials in the SR; whether or not they have presented the SR at a scientific conference; whether or not they have submitted the SR to any journals; and main barriers to publish the SR. All survey will be administered using Google Form (https://www.google.com/intl/en/forms/about).

Sample size

Assuming that approximately 50% of the eligible protocols are not published, we would need a total of 220 studies to be able to detect a difference in the proportion of presence of statistically significant outcomes of 80% versus 60% with a type I error of 0.05 (two-sided) and a type II error of 0.10. We aim to repeat the random sampling of relevant studies from PROSPERO until the number of eligible studies reaches 220, or the registry is exhausted. The sample size will be modified depending on the actual proportion of unpublished reviews among the eligible protocols in our first batch.

Data analysis

Primary analyses

Our primary outcomes are two. The first is (i) proportion of SRs published in journal articles. We will examine the association between statistically significant findings and publication using univariate logistic regression. We will then use multivariate logistic regression models to adjust for two apparent confounders, namely the number of included

studies and year of registration. Another primary outcome is (ii) time from protocol registration to publication of SRs in journal articles, defined as time from the registration date to the acceptance date. We will draw Kaplan-Meier curves for time to publication, classified by SRs with and without statistically significant meta-analysis results. We will examine the association of statistical significance and time to publication using Log-rank test. We will use Cox proportional hazard model for a multivariate analysis to adjust for the number of included studies and year of registration.

Secondary analyses

Secondary outcomes will include (iii) a composite outcome of full-publication or presentation at scientific conferences, and (iv) submission to any journals. We will describe the proportion of statistical significance and summarize the characteristics of included SRs classified by full publication, submission, presentation, and no dissemination. We will analyse the association between statistically significant findings and the secondary outcomes using the same univariate logistic regression, multivariate logistic regression, Kaplan-Meier curves and Cox regression as the primary outcomes.

When there is a statistically significant association between statistically significant findings and the proportion or time to publication, we will explore the associated factors. We will examine the association of the proportion or time to publication with academic or financial COI, experience of SR publication, country of contact author's affiliation (English speaking or not), or multinational collaboration using Log-rank test. Additionally, we will use Cox proportional hazard model to explore the strongest factors associated with SR publication. We will summarize proportion of SRs that have not reported the primary outcomes as defined in the protocol among published SRs. We will

describe whether or not the PROSPERO status reflect the true publication status and will summarize the barriers for completed SRs to publish.

Sensitivity analysis

We will conduct the following pre-specified sensitivity analysis;

i) Restricting SRs to those in which the authors have clearly pre-defined primary outcomes including the time point of measurement in their protocols

## ETHICS AND DISSEMINATION

Ethics approval will be obtained from the Ethical Committee of the Kyoto University Graduate School of Medicine. This protocol has been registered in the University hospital Medical Information Network (UMIN) Clinical Trials Registry (This protocol will be registered in the UMIN after all authors read and agree with the manuscript. Trial registration number will be appended here). We will publish our findings in a peer-reviewed journal and also may present them at conferences.

## DISCUSSION

SRs with adequate quality have potentials to alter the daily clinical practice, and are useful resources in developing clinical practice guidelines and policies. Publication bias and time lag bias can be a strong barrier to research transparency and integrity. Before the launch of PROSPERO, we did not have a tool to find SR protocols that remained unpublished. After six years from its launch, the registry will enable us to evaluate publication bias and time lag bias in the SR field, as was the case of clinical trial registries [7]. This is the first study to contact the authors of unpublished SRs and investigate the

existence and the magnitude of these biases. We recently suggested that protocol registration was not associated with reporting of statistical significance [15]. The factors associated with publication or time to publication of SRs will inform potential preventive measures for these biases. We also aim to describe the publication rate of registered protocols and the proportion of published SRs that have not reported primary outcomes as defined in the protocol, and check whether the PROSPERO status reflects the true publication status.

There are several expected limitations for this study. First, the generalizability will be limited because the analyses investigating the biases include only those who registered the protocol in the PROSPERO and respond to our survey. In order to increase the response rate, we will remind the contact authors up to 10 times for every week if they do not respond to our survey. Secondly, the time to publication may not reflect true time lag bias that is the period between the initiation of the SR and its publication because protocols may be registered after their analyses. The PROSPERO prohibits registration of completed reviews but some may nonetheless register after the completion of the analysis [16]. Because SRs that registered after their completion are more likely to have statistically significant findings and may be published earlier, if there are many such protocols, our hypothesized association may be overestimated. Thirdly, there can be unmeasurable confounding such as the methodological quality of the protocol. We will therefore perform a sensitivity analysis to restrict studies that adequately pre-defined their primary outcomes.

In conclusion, this study will provide comprehensive investigation about publication bias and time lag bias in the realm of SRs using the first global registry for SRs [17]. The expected findings will show the needs and the key factors to prevent such biases.

Acknowledgement

We would like to thank Center for Reviews and Dissemination at University York, UK for managing the PROSPERO

Contributions

YTsuj and YTsut contributed equally to this work. YTsuj, Ytsut, HT, YK, YY, DP, GHG, SF, and TAF contributed to the conception and design of the research. YTsuj and TAF are fully responsible for writing the protocol. TAF supervised the research, and all authors gave final approval of the protocol before submission.

Funding

This study is supported in part by JSPS KAKENHI (Grant-in-Aid for Scientific Research) Grant Number 17K19808 to TAF.

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 research support from Mochida and Tanabe-Mitsubishi. All the other authors report no competing interests to declare.

**REFERENCES**

1. Stern JM, Simes RJ. Publication bias: evidence of delayed publication in a cohort study of clinical research projects. Bmj. 1997;315(7109):640-5.
2. Hopewell S, Loudon K, Clarke MJ, Oxman AD, Dickersin K. Publication bias

in clinical trials due to statistical significance or direction of trial results. Cochrane Database Syst Rev. 2009(1):MR000006.

3. Dickersin K, Min YI, Meinert CL. Factors influencing publication of research results. Follow-up of applications submitted to two institutional review boards. Jama. 1992;267(3):374-8.

4. Ioannidis JP. Effect of the statistical significance of results on the time to completion and publication of randomized efficacy trials. Jama. 1998;279(4):281-6.

5. Simes RJ. Publication bias: the case for an international registry of clinical trials. J Clin Oncol. 1986;4(10):1529-41.

6. Dickersin K. How important is publication bias? A synthesis of available data. AIDS education and prevention : official publication of the International Society for AIDS Education. 1997;9(1 Suppl):15-21.

7. Song F, Parekh S, Hooper L, Loke YK, Ryder J, Sutton AJ, et al. Dissemination and publication of research findings: an updated review of related biases. Health Technol Assess. 2010;14(8):iii, ix-xi, 1-193.

8. Higgins JP, Green S, (editors). Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 [updated March 2011]. The Cochrane Collaboration. 2011.

9. Dickersin K, Olson CM, Rennie D, Cook D, Flanagin A, Zhu Q, et al. Association between time interval to publication and statistical significance. Jama. 2002;287(21):2829-31.

10. Mueller KF, Meerpohl JJ, Briel M, Antes G, von Elm E, Lang B, et al. Methods for detecting, quantifying, and adjusting for dissemination bias in meta-analysis are described. J Clin Epidemiol. 2016;80:25-33.

11. Tricco AC, Pham B, Brehaut J, Tetroe J, Cappelli M, Hopewell S, et al. An international survey indicated that unpublished systematic reviews exist. J Clin Epidemiol. 2009;62(6):617-23 e5.

12. Tricco AC, Moher D, Chen MH, Daniel R. Factors predicting completion and time to publication of Cochrane reviews. Open medicine : a peer-reviewed, independent, open-access journal. 2009;3(4):e210-4.

13. Tricco AC, Tetzlaff J, Pham B, Brehaut J, Moher D. Non-Cochrane vs. Cochrane reviews were twice as likely to have positive conclusion statements: cross-sectional study. J Clin Epidemiol. 2009;62(4):380-6 e1.

14. Tsujimoto H, Tsujimoto Y, Kataoka Y. Unpublished systematic reviews and financial support: a meta-epidemiological study (abstract). XXIV Cochrane Colloquium; 2016 Oct 23-27; Seoul, South Korea 2016. In press.

15. Tsujimoto Y, Tsujimoto H, Kataoka Y, Kimachi M, Shimizu S, Ikenoue T, et al. Majority of systematic reviews published in high-impact journals neglected to register the protocols: a meta-epidemiological study. J Clin Epidemiol. 2017.

16. Dissemination CfRa. PROSPERO, International prospective register of systematic reviews [Available from: https://www.crd.york.ac.uk/prospero/.

17. Davies S. The importance of PROSPERO to the National Institute for Health Research. Systematic reviews. 2012;1:5.

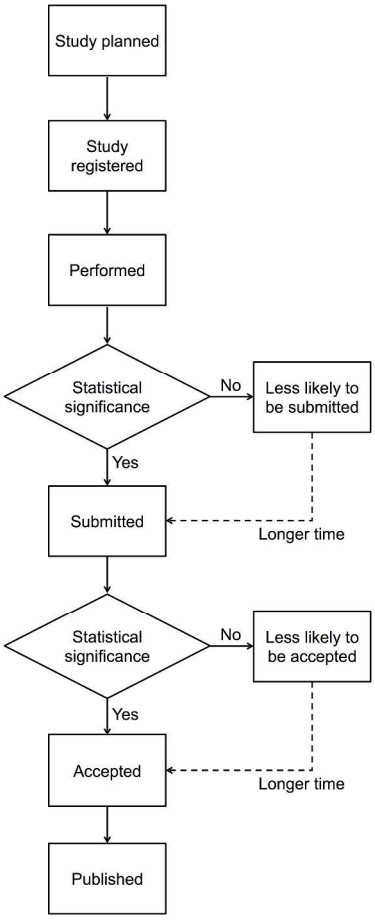


Figure 1. Concept of the present study
Study with statistical significant findings may be more likely to be submitted, accepted, and published (publication bias) and published earlier (time lag bias).

Figure 1. Concept of the present study
Study with statistical significant findings may be more likely to be submitted, accepted, and published (publication bias) and published earlier (time lag bias).

297x420mm (300 x 300 DPI)

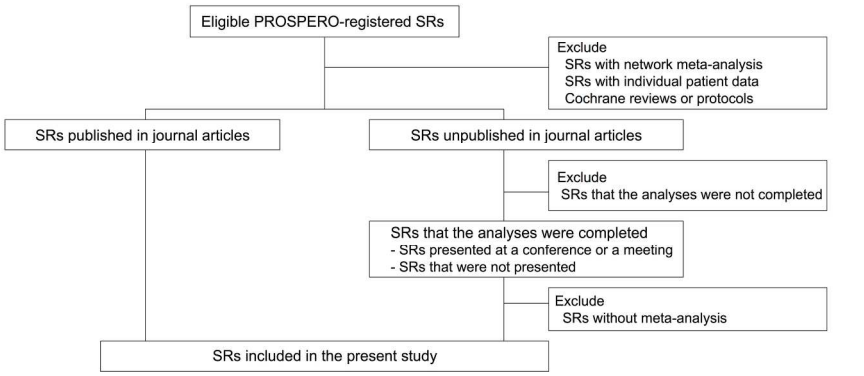


Figure 2. Expected flow diagram of the present study
PROSPERO = the international prospective register of systematic reviews, SR = systematic review, IPD = individual patient data

Figure 2. Expected flow diagram of the present study
PROSPERO = the international prospective register of systematic reviews, SR = systematic review, IPD = individual patient data

209x148mm (300 x 300 DPI)

BMJ Open

# Association between statistical significance and time to publication among systematic reviews: a study protocol for a meta-epidemiological investigation



| | |
|---|---|
| Journal: | *BMJ Open* |
| Manuscript ID | bmjopen-2017-018856.R1 |
| Article Type: | Protocol |
| Date Submitted by the Author: | 08-Sep-2017 |
| Complete List of Authors: | Tsujimoto, Yasushi ; School of Public Health in the Graduate School of Medicine, Kyoto University, Department of Healthcare Epidemiology; Kyoritsu Hospital, Department of Nephrology and Dialysis<br>Tsutsumi, Yusuke; School of Public Health in the Graduate School of Medicine, Kyoto University, Department of Healthcare Epidemiology<br>Kataoka, Yuki; School of Public Health in the Graduate School of Medicine, Kyoto University, Department of Healthcare Epidemiology<br>Tsujimoto, Hiraku; Hyogo Prefectural Amagasaki General Medical Center, Hospital Care Research Unit<br>Yamamoto, Yosuke; School of Public Health in the Graduate School of Medicine, Kyoto University, Department of Healthcare Epidemiology<br>Papola, Davide; University of Verona, WHO Collaborating Centre for Research and Training in Mental Health and Service Evaluation; Department of Neuroscience, Biomedicine and Movement Sciences; Section of Psychiatry<br>Guyatt, Gordon; Mcmaster University, Department of Health Research Methods, Evidence and Impact<br>Fukuhara, Shunichi; School of Public Health in the Graduate School of Medicine, Kyoto University, Department of Healthcare Epidemiology<br>Furukawa, Toshi; School of Public Health in the Graduate School of Medicine, Kyoto University, Department of Health Promotion and Human Behavior |
| Primary Subject Heading: | Epidemiology |
| Secondary Subject Heading: | Medical publishing and peer review |
| Keywords: | publication bias, time lag bias, systematic reviews, protocol registration, meta-epidemiological study |
| | |

**Title page**

**Title**

Association between statistical significance and time to publication among systematic reviews: a study protocol for a meta-epidemiological investigation

**Authors:**

Yasushi Tsujimoto[1,2], yssh0108@yahoo.co.jp

Yusuke Tsutsumi[1], patachan03@yahoo.co.jp

Yuki Kataoka[1], youkiti@gmail.com

Hiraku Tsujimoto[3], hira.to.ber3598@gmail.com

Yosuke Yamamoto[1], yamamoto.yosuke.5n@kyoto-u.ac.jp

Davide Papola[4], candido09@hotmail.it

Gordon H Guyatt[5], guyatt@mcmaster.ca

Shunichi Fukuhara[1], fukuhara.shunichi.6m@kyoto-u.ac.jp

Toshi A Furukawa[6], furukawa@kuhp.kyoto-u.ac.jp

**Affiliations:**

1. Department of Healthcare Epidemiology, School of Public Health in the Graduate School of Medicine, Kyoto University, Yoshida Konoe-cho, Sakyo-ku, Kyoto 606-8501, Japan
2. Department of Nephrology and Dialysis, Kyoritsu Hospital, 16-5 Chuo-cho, Kawanishi, Hyogo 666-0016, Japan
3. Hospital Care Research Unit, Hyogo Prefectural Amagasaki General Medical Center, 2-17-77 Higashi-Naniwa-Cho, Amagasaki, Hyogo 660-8550, Japan

4. WHO Collaborating Centre for Research and Training in Mental Health and Service Evaluation; Department of Neuroscience, Biomedicine and Movement Sciences; Section of Psychiatry, University of Verona, Verona, Italy
5. Department of Health Research Methods, Evidence and Impact, McMaster University, Hamilton, ON L8S 4K1, Canada.
6. Department of Health Promotion and Human Behavior, School of Public Health in the Graduate School of Medicine, Kyoto University, Yoshida Konoe-cho, Sakyo-ku, Kyoto 606-8501, Japan

**Corresponding author:**

Toshi A Furukawa

Department of Health Promotion and Human Behavior, School of Public Health in the Graduate School of Medicine, Kyoto University, Yoshida Konoe-cho, Sakyo-ku, Kyoto 606-8501, Japan

Phone: +81-75-753-9491

Fax: +81-75-753-4641

Email: furukawa@kuhp.kyoto-u.ac.jp

**Word count: 2506**

## Abstract

### Introduction

Many studies have indicated the impact of bias in dissemination and publication in medical research. Existence of such bias among clinical trials has been repeatedly pointed out, but it has not been well studied in the field of systematic reviews (SRs). We therefore aim to investigate whether or not time lag bias and publication bias in SRs based on statistical significance in results exist. In addition, we will examine at what stage of paper publication process such bias, if any, creeps in.

### Method and analysis

The present study is a meta-epidemiological study. We will include all SRs of interventions registered in the international prospective register of systematic reviews (PROSPERO) before Dec 2014 if the SR has completed its analysis irrespective of its publication status. All contact authors of eligible SRs will be asked to participate in a survey administered through the Internet. Our primary outcome is time from protocol registration to full publication of SR as a journal article, defined as time from the registration date to the acceptance date among all the relevant SRs. We will examine the impact of statistically significant findings on the primary outcomes through time to event analyses.

### Ethics and dissemination

Ethics approval will be obtained from the Ethical Committee of the Kyoto University Graduate School of Medicine. This protocol has been registered in the University hospital Medical Information Network (UMIN) Clinical Trials Registry. We will publish our

findings in a peer-reviewed journal and also may present them at conferences.

**Trial registration number: UMIN000028325**

## Strengths and limitations of this study

- This is the first study to contact the authors of unpublished systematic reviews (SRs) and investigate the existence and the magnitude of time lag bias in the realm of SRs.
- The factors associated with time to publication of SRs will inform potential preventive measures for these biases
- The generalizability will be limited because the analyses investigating the biases include only those who registered the protocol in the PROSPERO and respond to our survey
- The time to publication may not reflect true time lag bias that is the period between the initiation of the SR and its publication because protocols may be registered after their analyses

## INTRODUCTION

Many studies have reported bias in dissemination and publication of research findings in medicine [1-5]. Bias in dissemination and publication can be introduced at all stages of the publication process after study commencement, such as conducting research and writing up of manuscripts by investigators, and acceptance by journal editors or peer-reviewers.

Publication bias occurs when the authors' decision to write and submit the results or editors' acceptance for publication is influenced by the direction or strength of the study findings [6]. When this happens, findings of published studies will be systematically different from those of unpublished studies and hence from the underlying truth (Figure 1) [7].

Time lag bias is one aspect of publication bias which arises when the speed of publication depends on the direction and nature of the results [2, 7, 8]. In randomized clinical trials (RCTs), trials without statistical significant results take a longer time before publication than trials with statistical significant results (Figure 1) [4]. Prior studies found that publication bias is often due to investigators' failure to write up and submit rather than due to editors or reviewers [7, 9]. With respect to time lag in particular, one can characterize the phenomenon as either delay due to non-significant results, or expedited submission and publication due to significant results.

Bias in dissemination and publication among clinical trials has been well studied, however it has not been much studied in the field of non-Cochrane SRs [10]. A study suggested that statistical significant results were not associated with time to publication of Cochrane reviews [11]. This result may not apply non-Cochrane reviews because several studies suggested that there were deference in the quality of reporting between

Cochrane and non-Cochrane reviews [12, 13]. A survey among first or corresponding authors of SRs indicated that unpublished SRs exist [14]. The authors reported common reasons for not publishing SRs including lack of time and the manuscript being rejected by journals. Statistical significance was not reported as being a major barrier or reason for not publishing, but 65% of respondents reported significant results as a significant facilitator for publishing SRs – in other words authors are more likely, faced with other pressures, to take the time to complete and submit their review when they have positive results to report. Moreover, non-Cochrane SRs were likely to report statistical significance findings and positive conclusions [13]. We recently reported more than 30% of non-Cochrane SRs registered in the international prospective register of systematic reviews (PROSPERO) were not published after at least 50 months of registration [15]. These results indicate that time lag bias and publication bias among non-Cochrane SRs may well exist.

This study therefore aims to investigate whether or not time lag bias and publication bias in SRs based on statistical significance exist. We will also evaluate other factors associated with time to publication.

## OBJECTIVES

We aim to evaluate the association between statistical significance of meta-analysis result and publication status using a number of criteria (full publication in a journal article, submission to any journals, presentation of an abstract at a meeting) among SRs. We also aim to examine other factors of possible influence and publication of SRs.

## METHODS AND ANALYSIS

Inclusion and exclusion criteria

All SR protocols of interventions registered in the PROSPERO by 31st Dec 2014 will be eligible. We have chosen this time limit because we expect that it may often take 3 years to complete and publish SR after its registration [15] . We will exclude SRs that include studies other than RCT. We will exclude SRs whose analysis has not been completed and SRs without quantitative synthesis. We will exclude Cochrane protocols and reviews because their publication process is different from general peer-reviewed journals. We will also exclude SRs of diagnostic test accuracy and prognosis, and SRs with network meta-analysis, individual patient data meta-analyses because different factors are likely to be at play. Figure 2 shows the expected flow diagram of this study.

Search method

We will search the relevant SRs in the PROSPERO. The planned start date of the search will be on November 15th 2017. We will use search filters of "Exclude Cochrane protocols" for type of protocol and "Intervention, Prevention or Service Delivery" for type and method of the review. For protocols with "Ongoing and Completed" stage of review, we will search MEDLINE via PubMed and Google Scholar to find a full publication, using the authors' names and the keywords for participants or intervention in the PROSPERO because our pilot search indicated the status of the PROSPERO may often not be updated promptly to reflect the true status. For protocols with "Abandoned" stage of review, we will exclude them when their data analyses have not been completed.

Study selection

The selected studies based on a random sample of 500 of the PROSPERO records

identified by the initial search will be divided into two sets and two pairs of assessors (YTsuj, YTsut, HT, and YK) will assess the eligibility for each set separately. We will resolve disagreements by discussion between the authors, with another author (TAF) acting as an arbiter.

Data extraction

All records of included SR protocols will be downloaded from the PROSPERO for the use of data extraction. Four authors (YTsuj, YTsut, DP, and YK) will independently extract the following data from the relevant SRs in the PROSPERO: Registration and anticipated date of completion, the number of authors, funding sources, conflicts of interests (COIs), stage of review, year of registration, and countries that the study has been conducted. We will define the primary review question of the SR in terms of participant, intervention, comparator, and primary outcome. As the review may provide several comparisons for the same class of interventions and comparators, we will define the primary comparison as the intervention and comparator that are described as the primary or the first one in the intervention and comparator section in the PROSPERO record, and the primary outcomes as all outcomes listed in the primary outcome section of PROSPERO. If the primary outcome was analyzed for multiple time points, we will use the meta-analysis result that included the largest number of studies. Should the primary outcome be missing in the primary outcome section of PROSPERO, we will define the one mentioned first as the primary outcome. For SRs published in a journal article, we will extract the date of acceptance. We choose acceptance date rather than publication date because the interval between acceptance date and publication date depends on many external factors unrelated to publication bias. If acceptance date is not available, we will

use the publication date for SRs published in open access journals, and the date of online publication ahead of print for SRs published in other journals. We will contact the authors or the editorial office if the relevant date is missing.

Survey

For potentially eligible SRs, we will contact the authors listed in the "Contact details for further information" of the PROSPERO records and will ask them to respond to a survey through the Internet. Through the survey, all contact authors of potentially eligible unpublished SRs will be asked whether or not the SR analysis has been completed. Additionally, all contact authors of published or completed but not published SRs will be asked the following information; whether or not each of the primary outcomes in the primary comparison (as defined by a decision rule described in Data extraction section above) was statistically significant; the review team's involvement in any of the trials included in the SR; the author's experience to publish an SR as a lead author before the PROPERO registration; relationship with a private for-profit consulting firm for SRs; and main barriers to publish the SR according to a classification used in a previous study [14]. In addition, we will ask if someone has published a review addressing the same question. If the authors have completed the analysis but not published it, the following information will be sought; the number of included trials in the SR; whether or not they have presented the SR at a scientific conference; and whether or not they have submitted the SR to any journals. All survey will be administered using Google Form (https://www.google.com/intl/en/forms/about). We will send a reminder along with the Google form link one week after the initial contact. If the authors have not responded by

that time, we will repeat this process twice.

Sample size

Based on previous findings, we estimate that proportion of statistical significance is approximately 50% among SRs registered in the PROSPERO, and the median time to publication are 15 months for SRs with statistical significance and 25 months for SRs without statistical significance [7, 13, 15, 16]. A total of 110 events is expected to provide approximately 90% power to detect the difference with an assumed type I error of 0.05 (two-sided). Assuming that approximately 50% of the eligible protocols are not published, we would need a total of 220 SRs. We aim to repeat the random sampling of relevant SRs from PROSPERO until the number of eligible SRs whose authors respond to our survey reaches 220, or the registry is exhausted. The sample size will be modified when the actual proportion of unpublished reviews among the eligible protocols in our first batch is less than 30% or more than 70%.

Data analysis

Primary analyses

Our primary outcome is (i) time from protocol registration to publication of SRs in journal articles, defined as time (months) from the registration date to the acceptance date. We will draw Kaplan-Meier curves for time to publication, classified by SRs with and without statistically significant meta-analysis results. We will examine the association of statistical significance and time to publication using Log-rank test. We will then use Cox proportional hazard model for a multivariable analysis to adjust for two apparent confounders, namely the number of included studies and year of registration. The number

of included studies possibly associates with the importance of the topic, and the increase of statistical power. The year of registration may associate with the effect size of the intervention, and the acceptance rate of SRs.

Secondary analyses

Secondary outcomes will include (ii) proportion of SR published in journal articles, (iii) a composite outcome of full-publication or presentation at scientific conferences, and (iv) submission to any journals. We will describe a table showing the proportion of statistical significance and summarize the characteristics of included SRs classified by full publication, submission, presentation, and no dissemination. We will analyse the association between statistically significant findings and the secondary outcomes using univariable logistic regression, and multivariable logistic regression to adjust for the number of included studies and year of registration.

When there is a statistically significant association between statistically significant findings and time to publication, we will explore the predictors of time to publication other than statistical significance, number of included studies, and year of publication. First, we will examine the association of the proportion or time to publication with academic or financial COI, experience of SR publication, country of contact author's affiliation (English speaking or not), or multinational collaboration using Log-rank test. Then, we will use Cox proportional hazard model to explore the influence of these factors on the association between statistical significance and time to publication. We will summarize proportion of SRs that have not reported the primary outcomes as defined in the protocol among published SRs. We will describe whether or not the PROSPERO status reflect the true publication status and will summarize the barriers for completed

SRs to publish.

Continuous variables will be shown as mean (standardized deviation) and categorical variables will be expressed as numbers with percentage (%). A two-sided *p*-value smaller than 0.05 will be considered statistical significance. We will use Stata/SE, version 14.0 (StataCorp, College Station, TX, USA) for all analyses.

Sensitivity analysis

We will conduct the following pre-specified sensitivity analysis;

i) Restricting SRs to those in which the authors have clearly pre-defined primary outcomes including the time point of measurement in their protocols

## ETHICS AND DISSEMINATION

Ethics approval will be obtained from the Ethical Committee of the Kyoto University Graduate School of Medicine. This protocol has been registered in the University hospital Medical Information Network (UMIN) Clinical Trials Registry (This protocol will be registered in the UMIN after all authors read and agree with the manuscript. Trial registration number will be appended here). The planned completion date of the present study is December 31, 2018. We will publish our findings in a peer-reviewed journal and also may present them at conferences.

## DISCUSSION

SRs with adequate quality have potentials to alter the daily clinical practice, and are useful resources in developing clinical practice guidelines and policies. Time lag bias and publication bias can be a strong barrier to research transparency and integrity. Before the

launch of PROSPERO, it was difficult to find SR protocols that remained unpublished. After six years from its launch, the registry will enable us to evaluate publication bias and time lag bias in the SR field, as was the case of clinical trial registries [7]. This is the first study to contact the authors of unpublished SRs and investigate the existence and the magnitude of these biases. We recently suggested that protocol registration was not associated with reporting of statistical significance [16]. The factors associated with publication or time to publication of SRs will inform potential preventive measures for these biases. We also aim to describe the publication rate of registered protocols and the proportion of published SRs that have not reported primary outcomes as defined in the protocol, and check whether the PROSPERO status reflects the true publication status.

There are several expected limitations for this study. First, the generalizability will be limited because the analyses investigating the biases include only those who registered the protocol in the PROSPERO and respond to our survey. In order to increase the response rate, we will remind the contact authors up to 2 times for every week if they do not respond to our survey. Secondly, the time to publication may not reflect true time lag bias that is the period between the initiation of the SR and its publication because protocols may be registered after their analyses. The PROSPERO prohibits registration of completed reviews but some may nonetheless register after the completion of the analysis [17]. Because SRs that registered after their completion are more likely to have statistically significant findings and may be published earlier, if there are many such protocols, our hypothesized association may be overestimated. Thirdly, there can be unmeasurable confounding such as the methodological quality of the protocol. We will therefore perform a sensitivity analysis to restrict studies that adequately pre-defined their primary outcomes. Finally, unlike clinical trials, the authors may not intend to find

statistical significance in the realm of SRs. This may bias the association the between statistical significance and publication towards null.

In conclusion, this study will provide comprehensive investigation about time lag bias and publication bias in the realm of SRs using the first global registry for SRs [18]. The expected findings will show the needs and the key factors to prevent such biases.

Acknowledgement

We would like to thank Center for Reviews and Dissemination at University York, UK for managing the PROSPERO

Contributions

YTsuj and YTsut contributed equally to this work. YTsuj, Ytsut, HT, YK, YY, DP, GHG, SF, and TAF contributed to the conception and design of the research. YTsuj and TAF are fully responsible for writing the protocol. TAF supervised the research, and all authors gave final approval of the protocol before submission.

After the publication of the protocol, we plan the following contributions of each author: YTsuj, Ytsut, HT, YK, and DP will screen the relevant records of the PROSPERO, and extract data. YTsuj, Ytsut, HT, YK, DP, GHG, and TAF will contact the authors for additional information. YTsuj, Ytsut, YY, and TAF will conduct the data analysis without blinding of the data. YTsuj, Ytsut and TAF will write the manuscript. GHG, SF, and TAF will revise the manuscript critically for important intellectual content. TAF will supervise the research.

Funding

This study is supported in part by JSPS KAKENHI (Grant-in-Aid for Scientific Research) Grant Number 17K19808 to TAF. The funder plays no role in developing the 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 research support from Mochida and Tanabe-Mitsubishi. All the other authors report no competing interests to declare.

**REFERENCES**

1. Stern JM, Simes RJ. Publication bias: evidence of delayed publication in a cohort study of clinical research projects. Bmj. 1997;315(7109):640-5.
2. Hopewell S, Loudon K, Clarke MJ, Oxman AD, Dickersin K. Publication bias in clinical trials due to statistical significance or direction of trial results. Cochrane Database Syst Rev. 2009(1):MR000006.
3. Dickersin K, Min YI, Meinert CL. Factors influencing publication of research results. Follow-up of applications submitted to two institutional review boards. Jama. 1992;267(3):374-8.
4. Ioannidis JP. Effect of the statistical significance of results on the time to completion and publication of randomized efficacy trials. Jama. 1998;279(4):281-6.
5. Simes RJ. Publication bias: the case for an international registry of clinical trials. J Clin Oncol. 1986;4(10):1529-41.
6. Dickersin K. How important is publication bias? A synthesis of available data. AIDS education and prevention : official publication of the International Society for AIDS Education. 1997;9(1 Suppl):15-21.
7. Song F, Parekh S, Hooper L, Loke YK, Ryder J, Sutton AJ, et al. Dissemination and publication of research findings: an updated review of related biases.

Health Technol Assess. 2010;14(8):iii, ix-xi, 1-193.

8. Higgins JP, Green S, (editors). Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 [updated March 2011]. The Cochrane Collaboration. 2011.

9. Dickersin K, Olson CM, Rennie D, Cook D, Flanagin A, Zhu Q, et al. Association between time interval to publication and statistical significance. Jama. 2002;287(21):2829-31.

10. Mueller KF, Meerpohl JJ, Briel M, Antes G, von Elm E, Lang B, et al. Methods for detecting, quantifying, and adjusting for dissemination bias in meta-analysis are described. J Clin Epidemiol. 2016;80:25-33.

11. Tricco AC, Moher D, Chen MH, Daniel R. Factors predicting completion and time to publication of Cochrane reviews. Open medicine : a peer-reviewed, independent, open-access journal. 2009;3(4):e210-4.

12. Tricco AC, Tetzlaff J, Pham B, Brehaut J, Moher D. Non-Cochrane vs. Cochrane reviews were twice as likely to have positive conclusion statements: cross-sectional study. J Clin Epidemiol. 2009;62(4):380-6 e1.

13. Moher D, Tetzlaff J, Tricco AC, Sampson M, Altman DG. Epidemiology and reporting characteristics of systematic reviews. PLoS Med. 2007;4(3):e78.

14. Tricco AC, Pham B, Brehaut J, Tetroe J, Cappelli M, Hopewell S, et al. An international survey indicated that unpublished systematic reviews exist. J Clin Epidemiol. 2009;62(6):617-23 e5.

15. Tsujimoto H, Tsujimoto Y, Kataoka Y. Unpublished systematic reviews and financial support: a meta-epidemiological study (abstract). XXIV Cochrane Colloquium; 2016 Oct 23-27; Seoul, South Korea [Available from: https://abstractscochraneorg/2016-seoul/unpublished-systematic-reviews-and-financial-support-meta-epidemiological-study]. 2016.

16. Tsujimoto Y, Tsujimoto H, Kataoka Y, Kimachi M, Shimizu S, Ikenoue T, et al. Majority of systematic reviews published in high-impact journals neglected to register the protocols: a meta-epidemiological study. J Clin Epidemiol. 2017.

17. Dissemination CfRa. PROSPERO, International prospective register of systematic reviews [Available from: https://www.crd.york.ac.uk/prospero/.

18. Davies S. The importance of PROSPERO to the National Institute for Health Research. Systematic reviews. 2012;1:5.

392

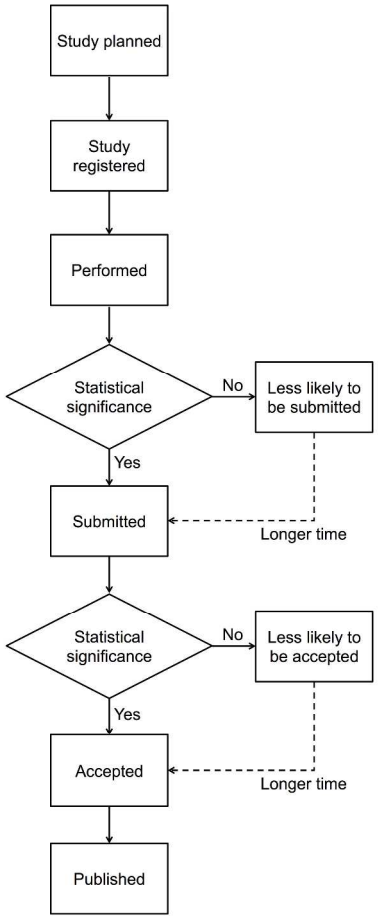


Figure 1. Concept of the present study
Study with statistical significant findings may be more likely to be submitted, accepted, and published (publication bias) and published earlier (time lag bias).

Figure 1. Concept of the present study
Study with statistical significant findings may be more likely to be submitted, accepted, and published (publication bias) and published earlier (time lag bias).

297x420mm (300 x 300 DPI)

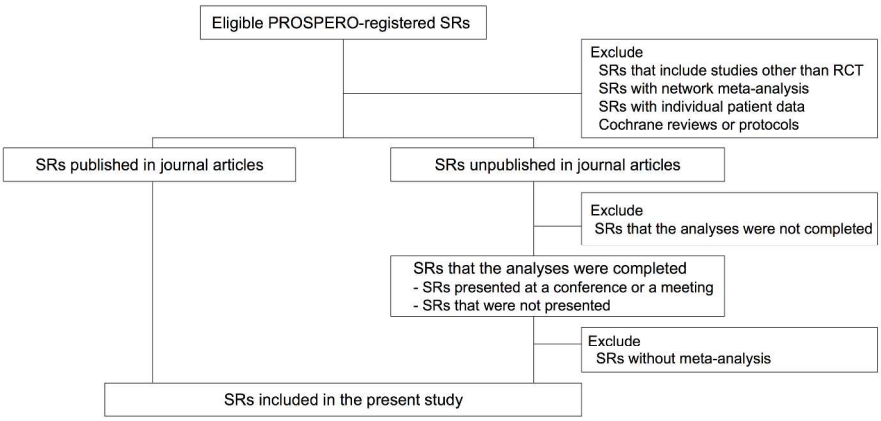


Figure 2. Expected flow diagram of the present study
PROSPERO = the international prospective register of systematic reviews, SR = systematic review, RCT = randomised controlled trial

Figure 2. Expected flow diagram of the present study‼ ┼
PROSPERO = the international prospective register of systematic reviews, SR = systematic review, RCT = randomised controlled trial

297x209mm (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 |
|---|---|---|
| **ADMINISTRATIVE INFORMATION** | | |
| Title: | | |
| Identification | 1a | Identify the report as a protocol of a systematic review Page 1 |
| Update | 1b | If the protocol is for an update of a previous systematic review, identify as such Not applicable (NA) |
| Registration | 2 | If registered, provide the name of the registry (such as PROSPERO) and registration number Page 4 |
| Authors: | | |
| Contact | 3a | Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author Page 1 |
| Contributions | 3b | Describe contributions of protocol authors and identify the guarantor of the review Page 14-15 |
| Amendments | 4 | If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments NA |
| Support: | | |
| Sources | 5a | Indicate sources of financial or other support for the review Page 15 |
| Sponsor | 5b | Provide name for the review funder and/or sponsor Page 15 |
| Role of sponsor or funder | 5c | Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol Page 15 |
| **INTRODUCTION** | | |
| Rationale | 6 | Describe the rationale for the review in the context of what is already known Page 5-6 |
| Objectives | 7 | Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO) Page 6 |
| **METHODS** | | |
| Eligibility criteria | 8 | Specify the study characteristics (such as PICO, study design, setting, time frame) and report characteristics (such as years considered, language, publication status) to be used as criteria for eligibility for the review Page 7 |
| Information sources | 9 | Describe all intended information sources (such as electronic databases, contact with study authors, trial registers or other grey literature sources) with planned dates of coverage Page 7 |
| Search strategy | 10 | Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated Page 7 |
| Study records: | | |
| Data management | 11a | Describe the mechanism(s) that will be used to manage records and data throughout the review Page 8-9 |

| | | |
|---|---|---|
| Selection process | 11b | State the process that will be used for selecting studies (such as two independent reviewers) through each phase of the review (that is, screening, eligibility and inclusion in meta-analysis) Page 8 |
| Data collection process | 11c | Describe planned method of extracting data from reports (such as piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators Page 8-9 |
| 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 Page 8-9 |
| Outcomes and prioritization | 13 | List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale Page 10 |
| 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 NA |
| Data synthesis | 15a | Describe criteria under which study data will be quantitatively synthesised NA |
| | 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 $\tau$) NA |
| | 15c | Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression) Page 12 |
| | 15d | If quantitative synthesis is not appropriate, describe the type of summary planned NA |
| Meta-bias(es) | 16 | Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies) NA |
| Confidence in cumulative evidence | 17 | Describe how the strength of the body of evidence will be assessed (such as GRADE) NA |

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

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

BMJ Open

# Association between statistical significance and time to publication among systematic reviews: a study protocol for a meta-epidemiological investigation



| | |
|---|---|
| Journal: | *BMJ Open* |
| Manuscript ID | bmjopen-2017-018856.R2 |
| Article Type: | Protocol |
| Date Submitted by the Author: | 27-Sep-2017 |
| Complete List of Authors: | Tsujimoto, Yasushi ; School of Public Health in the Graduate School of Medicine, Kyoto University, Department of Healthcare Epidemiology; Kyoritsu Hospital, Department of Nephrology and Dialysis<br>Tsutsumi, Yusuke; School of Public Health in the Graduate School of Medicine, Kyoto University, Department of Healthcare Epidemiology<br>Kataoka, Yuki; School of Public Health in the Graduate School of Medicine, Kyoto University, Department of Healthcare Epidemiology<br>Tsujimoto, Hiraku; Hyogo Prefectural Amagasaki General Medical Center, Hospital Care Research Unit<br>Yamamoto, Yosuke; School of Public Health in the Graduate School of Medicine, Kyoto University, Department of Healthcare Epidemiology<br>Papola, Davide; University of Verona, WHO Collaborating Centre for Research and Training in Mental Health and Service Evaluation; Department of Neuroscience, Biomedicine and Movement Sciences; Section of Psychiatry<br>Guyatt, Gordon; Mcmaster University, Department of Health Research Methods, Evidence and Impact<br>Fukuhara, Shunichi; School of Public Health in the Graduate School of Medicine, Kyoto University, Department of Healthcare Epidemiology<br>Furukawa, Toshi; School of Public Health in the Graduate School of Medicine, Kyoto University, Department of Health Promotion and Human Behavior |
| Primary Subject Heading: | Epidemiology |
| Secondary Subject Heading: | Medical publishing and peer review |
| Keywords: | publication bias, time lag bias, systematic reviews, protocol registration, meta-epidemiological study |
| | |

**Title page**

**Title**

Association between statistical significance and time to publication among systematic reviews: a study protocol for a meta-epidemiological investigation

**Authors:**

Yasushi Tsujimoto[1,2], yssh0108@yahoo.co.jp

Yusuke Tsutsumi[1], patachan03@yahoo.co.jp

Yuki Kataoka[1], youkiti@gmail.com

Hiraku Tsujimoto[3], hira.to.ber3598@gmail.com

Yosuke Yamamoto[1], yamamoto.yosuke.5n@kyoto-u.ac.jp

Davide Papola[4], candido09@hotmail.it

Gordon H Guyatt[5], guyatt@mcmaster.ca

Shunichi Fukuhara[1], fukuhara.shunichi.6m@kyoto-u.ac.jp

Toshi A Furukawa[6], furukawa@kuhp.kyoto-u.ac.jp

**Affiliations:**

1. Department of Healthcare Epidemiology, School of Public Health in the Graduate School of Medicine, Kyoto University, Yoshida Konoe-cho, Sakyo-ku, Kyoto 606-8501, Japan
2. Department of Nephrology and Dialysis, Kyoritsu Hospital, 16-5 Chuo-cho, Kawanishi, Hyogo 666-0016, Japan
3. Hospital Care Research Unit, Hyogo Prefectural Amagasaki General Medical Center, 2-17-77 Higashi-Naniwa-Cho, Amagasaki, Hyogo 660-8550, Japan

4. WHO Collaborating Centre for Research and Training in Mental Health and Service Evaluation; Department of Neuroscience, Biomedicine and Movement Sciences; Section of Psychiatry, University of Verona, Verona, Italy
5. Department of Health Research Methods, Evidence and Impact, McMaster University, Hamilton, ON L8S 4K1, Canada.
6. Department of Health Promotion and Human Behavior, School of Public Health in the Graduate School of Medicine, Kyoto University, Yoshida Konoe-cho, Sakyo-ku, Kyoto 606-8501, Japan

**Corresponding author:**

Toshi A Furukawa

Department of Health Promotion and Human Behavior, School of Public Health in the Graduate School of Medicine, Kyoto University, Yoshida Konoe-cho, Sakyo-ku, Kyoto 606-8501, Japan

Phone: +81-75-753-9491

Fax: +81-75-753-4641

Email: furukawa@kuhp.kyoto-u.ac.jp

**Word count: 2506**

## Abstract

### Introduction

Many studies have indicated the impact of bias in dissemination and publication in medical research. Existence of such bias among clinical trials has been repeatedly pointed out, but it has not been well studied in the field of systematic reviews (SRs). We therefore aim to investigate whether or not time lag bias and publication bias in SRs based on statistical significance in results exist. In addition, we will examine at what stage of paper publication process such bias, if any, creeps in.

### Method and analysis

The present study is a meta-epidemiological study. We will include all SRs of interventions registered in the international prospective register of systematic reviews (PROSPERO) before Dec 2014 if the SR has completed its analysis irrespective of its publication status. All contact authors of eligible SRs will be asked to participate in a survey administered through the Internet. Our primary outcome is time from protocol registration to full publication of SR as a journal article, defined as time from the registration date to the acceptance date among all the relevant SRs. We will examine the impact of statistically significant findings on the primary outcomes through time to event analyses.

### Ethics and dissemination

Ethics approval will be obtained from the Ethical Committee of the Kyoto University Graduate School of Medicine. This protocol has been registered in the University hospital Medical Information Network (UMIN) Clinical Trials Registry. We will publish our

findings in a peer-reviewed journal and also may present them at conferences.

**Trial registration number: UMIN000028325**

## Strengths and limitations of this study

- This is the first study to contact the authors of unpublished systematic reviews (SRs) and investigate the existence and the magnitude of time lag bias in the realm of SRs.
- The factors associated with time to publication of SRs will inform potential preventive measures for these biases
- The generalizability will be limited because the analyses investigating the biases include only those who registered the protocol in the PROSPERO and respond to our survey
- The time to publication may not reflect true time lag bias that is the period between the initiation of the SR and its publication because protocols may be registered after their analyses

## INTRODUCTION

Many studies have reported bias in dissemination and publication of research findings in medicine [1-5]. Bias in dissemination and publication can be introduced at all stages of the publication process after study commencement, such as conducting research and writing up of manuscripts by investigators, and acceptance by journal editors or peer-reviewers.

Publication bias occurs when the authors' decision to write and submit the results or editors' acceptance for publication is influenced by the direction or strength of the study findings [6]. When this happens, findings of published studies will be systematically different from those of unpublished studies and hence from the underlying truth (Figure 1) [7].

Time lag bias is one aspect of publication bias which arises when the speed of publication depends on the direction and nature of the results [2, 7, 8]. In randomized clinical trials (RCTs), trials without statistical significant results take a longer time before publication than trials with statistical significant results (Figure 1) [4]. Prior studies found that publication bias is often due to investigators' failure to write up and submit rather than due to editors or reviewers [7, 9]. With respect to time lag in particular, one can characterize the phenomenon as either delay due to non-significant results, or expedited submission and publication due to significant results.

Bias in dissemination and publication among clinical trials has been well studied, however it has not been much studied in the field of non-Cochrane SRs [10]. A study suggested that statistical significant results were not associated with time to publication of Cochrane reviews [11]. This result may not apply non-Cochrane reviews because several studies suggested that there were deference in the quality of reporting between

Cochrane and non-Cochrane reviews [12, 13]. A survey among first or corresponding authors of SRs indicated that unpublished SRs exist [14]. The authors reported common reasons for not publishing SRs including lack of time and the manuscript being rejected by journals. Statistical significance was not reported as being a major barrier or reason for not publishing, but 65% of respondents reported significant results as a significant facilitator for publishing SRs – in other words authors are more likely, faced with other pressures, to take the time to complete and submit their review when they have positive results to report. Moreover, non-Cochrane SRs were likely to report statistical significance findings and positive conclusions [13]. We recently reported more than 30% of non-Cochrane SRs registered in the international prospective register of systematic reviews (PROSPERO) were not published after at least 50 months of registration [15]. These results indicate that time lag bias and publication bias among non-Cochrane SRs may well exist.

This study therefore aims to investigate whether or not time lag bias and publication bias in SRs based on statistical significance exist. We will also evaluate other factors associated with time to publication.

## OBJECTIVES

We aim to evaluate the association between statistical significance of meta-analysis result and publication status using a number of criteria (full publication in a journal article, submission to any journals, presentation of an abstract at a meeting) among SRs. We also aim to examine other factors of possible influence and publication of SRs.

## METHODS AND ANALYSIS

Inclusion and exclusion criteria

All SR protocols of interventions registered in the PROSPERO by 31st Dec 2014 will be eligible. We have chosen this time limit because we expect that it may often take 3 years to complete and publish SR after its registration [15] . We will exclude SRs that include studies other than RCT. We will exclude SRs whose analysis has not been completed and SRs without quantitative synthesis. We will exclude Cochrane protocols and reviews because their publication process is different from general peer-reviewed journals. We will also exclude SRs of diagnostic test accuracy and prognosis, and SRs with network meta-analysis, individual patient data meta-analyses because different factors are likely to be at play. Figure 2 shows the expected flow diagram of this study.

Search method

We will search the relevant SRs in the PROSPERO. The planned start date of the search will be on November 15th 2017. We will use search filters of "Exclude Cochrane protocols" for type of protocol and "Intervention, Prevention or Service Delivery" for type and method of the review. For protocols with "Ongoing and Completed" stage of review, we will search MEDLINE via PubMed and Google Scholar to find a full publication, using the authors' names and the keywords for participants or intervention in the PROSPERO because our pilot search indicated the status of the PROSPERO may often not be updated promptly to reflect the true status. For protocols with "Abandoned" stage of review, we will exclude them when their data analyses have not been completed.

Study selection

The selected studies based on a random sample of 500 of the PROSPERO records

identified by the initial search will be divided into two subsamples of 250, and two pairs of assessors (YTsuj - YTsut, and HT - YK) will assess the eligibility for each set separately. We will resolve disagreements by discussion between the authors, with another author (TAF) acting as an arbiter.

Data extraction

All records of included SR protocols will be downloaded from the PROSPERO for the use of data extraction. Four authors (YTsuj, YTsut, DP, and YK) will independently extract the following data from the relevant SRs in the PROSPERO: Registration and anticipated date of completion, the number of authors, funding sources, conflicts of interests (COIs), stage of review, year of registration, and countries that the study has been conducted. We will define the primary review question of the SR in terms of participant, intervention, comparator, and primary outcome. As the review may provide several comparisons for the same class of interventions and comparators, we will define the primary comparison as the intervention and comparator that are described as the primary or the first one in the intervention and comparator section in the PROSPERO record, and the primary outcomes as all outcomes listed in the primary outcome section of PROSPERO. If the primary outcome was analyzed for multiple time points, we will use the meta-analysis result that included the largest number of studies. Should the primary outcome be missing in the primary outcome section of PROSPERO, we will define the one mentioned first as the primary outcome. For SRs published in a journal article, we will extract the date of acceptance. We choose acceptance date rather than publication date because the interval between acceptance date and publication date depends on many external factors unrelated to publication bias. If acceptance date is not available, we will

use the publication date for SRs published in open access journals, and the date of online publication ahead of print for SRs published in other journals. We will contact the authors or the editorial office if the relevant date is missing.

Survey

For potentially eligible SRs, we will contact the authors listed in the "Contact details for further information" of the PROSPERO records and will ask them to respond to a survey through the Internet. Through the survey, all contact authors of potentially eligible unpublished SRs will be asked whether or not the SR analysis has been completed. Additionally, all contact authors of published or completed but not published SRs will be asked the following information; whether or not each of the primary outcomes in the primary comparison (as defined by a decision rule described in Data extraction section above) was statistically significant; the review team's involvement in any of the trials included in the SR; the author's experience to publish an SR as a lead author before the PROPERO registration; relationship with a private for-profit consulting firm for SRs; and main barriers to publish the SR according to a classification used in a previous study [14]. In addition, we will ask if someone has published a review addressing the same question. If the authors have completed the analysis but not published it, the following information will be sought; the number of included trials in the SR; whether or not they have presented the SR at a scientific conference; and whether or not they have submitted the SR to any journals. All survey will be administered using Google Form (https://www.google.com/intl/en/forms/about). We will send a reminder along with the Google form link one week after the initial contact. If the authors have not responded by

that time, we will repeat this process twice.

Sample size

Based on previous findings, we estimate that proportion of statistical significance is approximately 50% among SRs registered in the PROSPERO, and the median time to publication are 15 months for SRs with statistical significance and 25 months for SRs without statistical significance [7, 13, 15, 16]. A total of 110 events is expected to provide approximately 90% power to detect the difference with an assumed type I error of 0.05 (two-sided). Assuming that approximately 50% of the eligible protocols are not published, we would need a total of 220 SRs. We aim to repeat the random sampling of relevant SRs from PROSPERO until the number of eligible SRs whose authors respond to our survey reaches 220, or the registry is exhausted. The sample size will be modified when the actual proportion of unpublished reviews among the eligible protocols in our first batch is less than 30% or more than 70%.

Data analysis

Primary analyses

Our primary outcome is (i) time from protocol registration to publication of SRs in journal articles, defined as time (months) from the registration date to the acceptance date. We will draw Kaplan-Meier curves for time to publication, classified by SRs with and without statistically significant meta-analysis results. We will examine the association of statistical significance and time to publication using Log-rank test. We will then use Cox proportional hazard model for a multivariable analysis to adjust for two apparent confounders, namely the number of included studies and year of registration. The number

of included studies possibly associates with the importance of the topic, and the increase of statistical power. The year of registration may associate with the effect size of the intervention, and the acceptance rate of SRs.

Secondary analyses

Secondary outcomes will include (ii) proportion of SR published in journal articles, (iii) a composite outcome of full-publication or presentation at scientific conferences, and (iv) submission to any journals. We will describe a table showing the proportion of statistical significance and summarize the characteristics of included SRs classified by full publication, submission, presentation, and no dissemination. We will analyse the association between statistically significant findings and the secondary outcomes using univariable logistic regression, and multivariable logistic regression to adjust for the number of included studies and year of registration.

When there is a statistically significant association between statistically significant findings and time to publication, we will explore the predictors of time to publication other than statistical significance, number of included studies, and year of publication. First, we will examine the association of the proportion or time to publication with academic or financial COI, experience of SR publication, country of contact author's affiliation (English speaking or not), or multinational collaboration using Log-rank test. Then, we will use Cox proportional hazard model to explore the influence of these factors on the association between statistical significance and time to publication. We will summarize proportion of SRs that have not reported the primary outcomes as defined in the protocol among published SRs. We will describe whether or not the PROSPERO status reflect the true publication status and will summarize the barriers for completed

SRs to publish.

Continuous variables will be shown as mean (standardized deviation) and categorical variables will be expressed as numbers with percentage (%). A two-sided *p*-value smaller than 0.05 will be considered statistical significance. We will use Stata/SE, version 14.0 (StataCorp, College Station, TX, USA) for all analyses.

Sensitivity analysis

We will conduct the following pre-specified sensitivity analysis;

i) Restricting SRs to those in which the authors have clearly pre-defined primary outcomes including the time point of measurement in their protocols

## ETHICS AND DISSEMINATION

Ethics approval will be obtained from the Ethical Committee of the Kyoto University Graduate School of Medicine. This protocol has been registered in the University hospital Medical Information Network (UMIN) Clinical Trials Registry (This protocol will be registered in the UMIN after all authors read and agree with the manuscript. Trial registration number will be appended here). The planned completion date of the present study is December 31, 2018. We will publish our findings in a peer-reviewed journal and also may present them at conferences.

## DISCUSSION

SRs with adequate quality have potentials to alter the daily clinical practice, and are useful resources in developing clinical practice guidelines and policies. Time lag bias and publication bias can be a strong barrier to research transparency and integrity. Before the

launch of PROSPERO, it was difficult to find SR protocols that remained unpublished. After six years from its launch, the registry will enable us to evaluate publication bias and time lag bias in the SR field, as was the case of clinical trial registries [7]. This is the first study to contact the authors of unpublished SRs and investigate the existence and the magnitude of these biases. We recently suggested that protocol registration was not associated with reporting of statistical significance [16]. The factors associated with publication or time to publication of SRs will inform potential preventive measures for these biases. We also aim to describe the publication rate of registered protocols and the proportion of published SRs that have not reported primary outcomes as defined in the protocol, and check whether the PROSPERO status reflects the true publication status.

There are several expected limitations for this study. First, the generalizability will be limited because the analyses investigating the biases include only those who registered the protocol in the PROSPERO and respond to our survey. In order to increase the response rate, we will remind the contact authors up to 2 times for every week if they do not respond to our survey. Secondly, the time to publication may not reflect true time lag bias that is the period between the initiation of the SR and its publication because protocols may be registered after their analyses. The PROSPERO prohibits registration of completed reviews but some may nonetheless register after the completion of the analysis [17]. Because SRs that registered after their completion are more likely to have statistically significant findings and may be published earlier, if there are many such protocols, our hypothesized association may be overestimated. Thirdly, there can be unmeasurable confounding such as the methodological quality of the protocol. We will therefore perform a sensitivity analysis to restrict studies that adequately pre-defined their primary outcomes. Fourth, the accuracy of PROSPERO filters is unknown, but the

use of these filters is not likely to bias the results of the present study. Finally, unlike clinical trials, the authors may not intend to find statistical significance in the realm of SRs. This may bias the association the between statistical significance and publication towards null.

In conclusion, this study will provide comprehensive investigation about time lag bias and publication bias in the realm of SRs using the first global registry for SRs [18]. The expected findings will show the needs and the key factors to prevent such biases.

Figure legend

Figure 1. Concept of the present study.□ Study with statistical significant findings may be more likely to be submitted, accepted, and published (publication bias) and published earlier (time lag bias).

Figure 2. Expected flow diagram of the present study

Acknowledgement

We would like to thank Center for Reviews and Dissemination at University York, UK for managing the PROSPERO

Contributions

YTsuj and YTsut contributed equally to this work. YTsuj, Ytsut, HT, YK, YY, DP, GHG, SF, and TAF contributed to the conception and design of the research. YTsuj and TAF are fully responsible for writing the protocol. TAF supervised the research, and all authors gave final approval of the protocol before submission.

After the publication of the protocol, we plan the following contributions of each author:

YTsuj, Ytsut, HT, YK, and DP will screen the relevant records of the PROSPERO, and extract data. YTsuj, Ytsut, HT, YK, DP, GHG, and TAF will contact the authors for additional information. YTsuj, Ytsut, YY, and TAF will conduct the data analysis without blinding of the data. YTsuj, Ytsut and TAF will write the manuscript. GHG, SF, and TAF will revise the manuscript critically for important intellectual content. TAF will supervise the research.

Funding

This study is supported in part by JSPS KAKENHI (Grant-in-Aid for Scientific Research) Grant Number 17K19808 to TAF. The funder plays no role in developing the 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 research support from Mochida and Tanabe-Mitsubishi. All the other authors report no competing interests to declare.

**REFERENCES**

1. Stern JM, Simes RJ. Publication bias: evidence of delayed publication in a cohort study of clinical research projects. Bmj. 1997;315(7109):640-5.
2. Hopewell S, Loudon K, Clarke MJ, Oxman AD, Dickersin K. Publication bias in clinical trials due to statistical significance or direction of trial results. Cochrane Database Syst Rev. 2009(1):MR000006.

3. Dickersin K, Min YI, Meinert CL. Factors influencing publication of research results. Follow-up of applications submitted to two institutional review boards. Jama. 1992;267(3):374-8.
4. Ioannidis JP. Effect of the statistical significance of results on the time to completion and publication of randomized efficacy trials. Jama. 1998;279(4):281-6.
5. Simes RJ. Publication bias: the case for an international registry of clinical trials. J Clin Oncol. 1986;4(10):1529-41.
6. Dickersin K. How important is publication bias? A synthesis of available data. AIDS education and prevention : official publication of the International Society for AIDS Education. 1997;9(1 Suppl):15-21.
7. Song F, Parekh S, Hooper L, Loke YK, Ryder J, Sutton AJ, et al. Dissemination and publication of research findings: an updated review of related biases. Health Technol Assess. 2010;14(8):iii, ix-xi, 1-193.
8. Higgins JP, Green S, (editors). Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 [updated March 2011]. The Cochrane Collaboration. 2011.
9. Dickersin K, Olson CM, Rennie D, Cook D, Flanagin A, Zhu Q, et al. Association between time interval to publication and statistical significance. Jama. 2002;287(21):2829-31.
10. Mueller KF, Meerpohl JJ, Briel M, Antes G, von Elm E, Lang B, et al. Methods for detecting, quantifying, and adjusting for dissemination bias in meta-analysis are described. J Clin Epidemiol. 2016;80:25-33.
11. Tricco AC, Moher D, Chen MH, Daniel R. Factors predicting completion and time to publication of Cochrane reviews. Open medicine : a peer-reviewed, independent, open-access journal. 2009;3(4):e210-4.
12. Tricco AC, Tetzlaff J, Pham B, Brehaut J, Moher D. Non-Cochrane vs. Cochrane reviews were twice as likely to have positive conclusion statements: cross-sectional study. J Clin Epidemiol. 2009;62(4):380-6 e1.
13. Moher D, Tetzlaff J, Tricco AC, Sampson M, Altman DG. Epidemiology and reporting characteristics of systematic reviews. PLoS Med. 2007;4(3):e78.
14. Tricco AC, Pham B, Brehaut J, Tetroe J, Cappelli M, Hopewell S, et al. An international survey indicated that unpublished systematic reviews exist. J Clin Epidemiol. 2009;62(6):617-23 e5.

15. Tsujimoto H, Tsujimoto Y, Kataoka Y. Unpublished systematic reviews and financial support: a meta-epidemiological study (abstract). XXIV Cochrane Colloquium; 2016 Oct 23-27; Seoul, South Korea [Available from: https://abstractscochraneorg/2016-seoul/unpublished-systematic-reviews-and-financial-support-meta-epidemiological-study]. 2016.

16. Tsujimoto Y, Tsujimoto H, Kataoka Y, Kimachi M, Shimizu S, Ikenoue T, et al. Majority of systematic reviews published in high-impact journals neglected to register the protocols: a meta-epidemiological study. J Clin Epidemiol. 2017.

17. Dissemination CfRa. PROSPERO, International prospective register of systematic reviews [Available from: https://www.crd.york.ac.uk/prospero/.

18. Davies S. The importance of PROSPERO to the National Institute for Health Research. Systematic reviews. 2012;1:5.

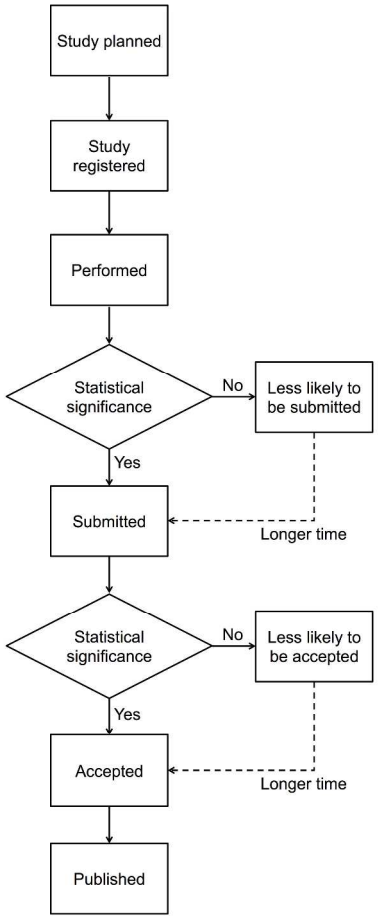


Figure 1. Concept of the present study
Study with statistical significant findings may be more likely to be submitted, accepted, and published (publication bias) and published earlier (time lag bias).

Figure 1. Concept of the present study
Study with statistical significant findings may be more likely to be submitted, accepted, and published (publication bias) and published earlier (time lag bias).

297x420mm (300 x 300 DPI)

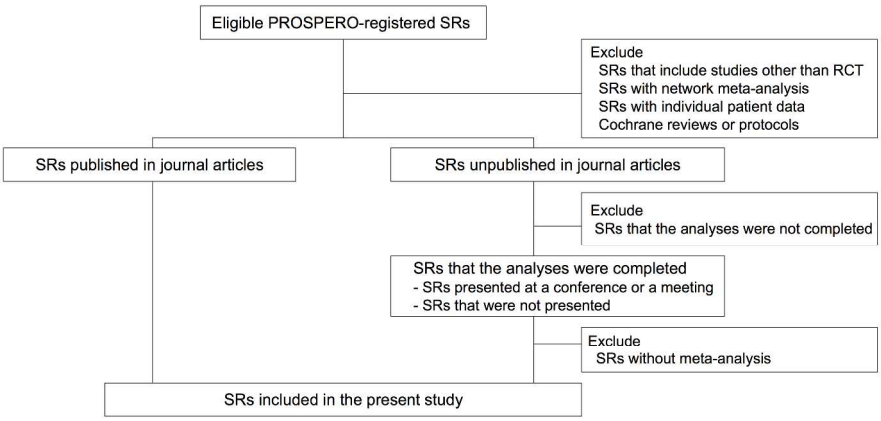


Figure 2. Expected flow diagram of the present study
PROSPERO = the international prospective register of systematic reviews, SR = systematic review, RCT = randomised controlled trial

Figure 2. Expected flow diagram of the present study‼ ┼
PROSPERO = the international prospective register of systematic reviews, SR = systematic review, RCT = randomised controlled trial

297x209mm (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 |
|---|---|---|
| **ADMINISTRATIVE INFORMATION** | | |
| Title: | | |
| Identification | 1a | Identify the report as a protocol of a systematic review Page 1 |
| Update | 1b | If the protocol is for an update of a previous systematic review, identify as such Not applicable (NA) |
| Registration | 2 | If registered, provide the name of the registry (such as PROSPERO) and registration number Page 4 |
| Authors: | | |
| Contact | 3a | Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author Page 1 |
| Contributions | 3b | Describe contributions of protocol authors and identify the guarantor of the review Page 14-15 |
| Amendments | 4 | If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments NA |
| Support: | | |
| Sources | 5a | Indicate sources of financial or other support for the review Page 15 |
| Sponsor | 5b | Provide name for the review funder and/or sponsor Page 15 |
| Role of sponsor or funder | 5c | Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol Page 15 |
| **INTRODUCTION** | | |
| Rationale | 6 | Describe the rationale for the review in the context of what is already known Page 5-6 |
| Objectives | 7 | Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO) Page 6 |
| **METHODS** | | |
| Eligibility criteria | 8 | Specify the study characteristics (such as PICO, study design, setting, time frame) and report characteristics (such as years considered, language, publication status) to be used as criteria for eligibility for the review Page 7 |
| Information sources | 9 | Describe all intended information sources (such as electronic databases, contact with study authors, trial registers or other grey literature sources) with planned dates of coverage Page 7 |
| Search strategy | 10 | Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated Page 7 |
| Study records: | | |
| Data management | 11a | Describe the mechanism(s) that will be used to manage records and data throughout the review Page 8-9 |

| | | |
|---|---|---|
| Selection process | 11b | State the process that will be used for selecting studies (such as two independent reviewers) through each phase of the review (that is, screening, eligibility and inclusion in meta-analysis) Page 8 |
| Data collection process | 11c | Describe planned method of extracting data from reports (such as piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators Page 8-9 |
| 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 Page 8-9 |
| Outcomes and prioritization | 13 | List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale Page 10 |
| 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 NA |
| Data synthesis | 15a | Describe criteria under which study data will be quantitatively synthesised NA |
| | 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 $\tau$) NA |
| | 15c | Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression) Page 12 |
| | 15d | If quantitative synthesis is not appropriate, describe the type of summary planned NA |
| Meta-bias(es) | 16 | Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies) NA |
| Confidence in cumulative evidence | 17 | Describe how the strength of the body of evidence will be assessed (such as GRADE) NA |

*** 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.*