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ORIGINAL ARTICLE

Statistical significance did not affect time to publication in non-Cochrane systematic reviews: a metaepidemiological study

Yasushi Tsujimoto[a,b], Yusuke Tsutsumi[a,c], Yuki Kataoka[a,d], Hiraku Tsujimoto[d], Yosuke Yamamoto[a], Davide Papola[e], Gordon H. Guyatt[f], Shunichi Fukuhara[a], Toshi A. Furukawa[g,*]

[a]*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*

[b]*Department of Nephrology and Dialysis, Kyoritsu Hospital, 16-5 Chuo-cho, Kawanishi, Hyogo 666-0016, Japan*

[c]*Department of Emergency Medicine, National Hospital Organization Mito Medical Center, 280 Sakuranosato Ibarakimachi Higasiibarakigun, Ibaraki, 311-3117, Japan*

[d]*Hospital Care Research Unit, Hyogo Prefectural Amagasaki General Medical Center, 2-17-77 Higashi-Naniwa-Cho, Amagasaki, Hyogo 660-8550, Japan*

[e]*Department of Neuroscience, WHO Collaborating Centre for Research and Training in Mental Health and Service Evaluation, Biomedicine and Movement Sciences, Section of Psychiatry, University of Verona, Verona, Italy*

[f]*Department of Health Research Methods, Evidence and Impact, McMaster University, Hamilton, ON L8S 4K1, Canada*

[g]*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*

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Abstract

Objectives: The objective of the study was to investigate time-lag bias based on statistical significance in findings in non-Cochrane systematic reviews (SRs) and explore barriers to publication for review authors.

Study Design and Setting: We included SRs of randomized controlled trials with completed analyses for protocols registered in the international prospective register of systematic reviews (PROSPERO) by the end of 2014. To obtain unpublished information, we sent questionnaires regarding barriers to publication of SRs to all authors between May and November 2018 and examined the association between the statistical significance of SR findings and time to acceptance.

Results: Among the 241 SR authors contacted, 141 (58%) responded, of whom 103 met the eligibility criteria and agreed to participate. Ninety-three (90%) of the protocols had been published as journal articles and 11 (11%) remained unpublished. Statistical significance was not significantly associated with time to acceptance (adjusted hazard ratio, 1.36; 95% confidence interval, 0.84 to 2.19). The authors reported lack of time (52%), rejection by journals (42%), duplication of similar topics (42%), and nonsignificant results (29%) as barriers to publication of SRs.

Conclusion: We found no convincing evidence of time-lag bias based on statistical significance in the findings among non-Cochrane SRs registered in the PROSPERO.

Keywords: Time-lag bias; Publication bias; Systematic review; Unpublished data

1. Introduction

Many studies have reported bias in the dissemination of findings from randomized controlled trials (RCTs) related to medical research [1−6]. This bias can lead to published studies reporting different results from those found by authors of unpublished studies, systematically producing biases in the literature that skew the overall estimates of RCT effects. Bias can arise at each stage of the dissemination process once data collection is complete, including manuscript preparation, investigator submission to journals,

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* Corresponding author. 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. Tel.: +81-75-753-9491; fax: +81-75-753-4641.

E-mail address: furukawa@kuhp.kyoto-u.ac.jp (T.A. Furukawa).

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What is new?

Key findings

- Ninety percent (93/103) of the non-Cochrane systematic reviews (SRs) with completed analyses were published within 3 years after registration in the international prospective register of systematic reviews (PROSPERO).
- Although we found no evidence to support statistical significance as a determinant of time to publication among non-Cochrane reviews, 29% of the review authors believed that nonsignificant results could be a barrier to publication.
- Lack of time, rejection by journals, and duplication of a similar topic were the most commonly reported barriers to publication of SRs.

What this study adds to what was known?

- This was the first systematic investigation of time-lag bias among non-Cochrane SRs.
- This study included published and unpublished data of non-Cochrane reviews and showed that there was no convincing evidence of time-lag bias based on statistical significance in SR findings.
- Our questionnaire exploring the barriers to publishing SRs found lack of time (52% [51/99]) and rejection by journals (42% [42/99]) were the most commonly reported obstacles to publishing SRs.
- 42% (42/99) of authors perceived duplication of a similar topic as a significant barrier to publishing SRs, although one of the aims of the PROSPERO was to reduce unintended duplication.

What was the implication and what should change now?

- Our failure to identify time-lag bias provides reassurance, although definitive conclusions will require a larger sample size and a higher response rate.
- We did not examine what happened to planned but nonregistered SRs, and our findings were based on the responses of review authors and therefore might not necessarily have been accurate or complete.
- Strategies to reduce duplications and development of supporting tools to minimize authors' tasks may be considered for promoting prompt SR publication.

journal acceptance of manuscripts, and citation of published studies.

Time-lag bias arises when delays in manuscript preparation and acceptance are related to the direction and nature of the results [1,7,8]. Several studies have found that RCTs without statistically significant results experience a longer time to publication than studies with statistically significant results [3]. Prior studies have found that the delay or failure to publish is often due to investigators' delay in preparing articles for submission rather than due to editors' or reviewers' rejection [7,8].

Time-lag bias among SRs is less well studied [9]. Furthermore, statistical significance has little importance for SR authors. In a previous study, SR authors reported that nonsignificant results seldom presented a barrier to publication [10]. Another study found no evidence of time-lag bias based on statistical significance among Cochrane reviews [11]. However, Cochrane reviews differ from non-Cochrane reviews in the quality of reporting, proportion of statistically significant results, and positive conclusions, all of which raise the possibility that the finding may not apply to non-Cochrane SRs [11−13].

In 2011, the U.K. Centre for Reviews and Dissemination founded the International Prospective Register of Systematic Reviews (PROSPERO) [14,15]. We had previously found some SRs registered in the PROSPERO that remained unpublished [16] but did not obtain unpublished results; thus, we were unable to explore whether the results had affected time to publication.

This study, therefore, aimed to investigate whether or not time-lag bias in SRs based on statistical significance exists and extracted not only published results but also unpublished results using surveys of SR authors who registered their protocol in the PROSPERO. In addition, we assessed whether statistically significant results could be an obstacle to publication for the SR authors and explored other barriers using survey questionnaires.

2. Materials and methods

The methods of this study have been described elsewhere [17]. We obtained ethics approval from the Ethical Committee of the Kyoto University Graduate School of Medicine (approval number, R1337). We also obtained informed consent from each participating author. The study was registered with UMIN-CTR as UMIN000028325 (https://upload.umin.ac.jp/cgi-open-bin/ctr/ctr_view.cgi?recptno = R000031688).

2.1. Inclusion and exclusion criteria

We included all SR protocols of interventions registered in the PROSPERO. Because it may take 3 years to complete and publish an SR after its registration [16], we

included all SR protocols registered as of December 31, 2014. We excluded SRs that included studies other than RCTs, SRs with incomplete analyses, SRs without quantitative synthesis, SRs of diagnostic test accuracy and prognosis, and SRs with network meta-analysis (NMA) or individual patient data (IPD) meta-analysis. We also excluded Cochrane reviews and SRs published in clinical practice guidelines (CPGs) or health technology assessments (HTAs).

2.2. Search method

We searched the relevant SRs in the PROSPERO on November 15, 2017. We used search filters of ''Exclude Cochrane protocols'' for type of protocol and ''Intervention, Prevention, or Service Delivery'' for type and method of the review. To find the publications, we hand-searched MEDLINE via PubMed and Google Scholar, using the keywords for participants or intervention and/or authors' names in the PROSPERO from January 3 to February 22, 2018.

2.3. Study selection and data extraction

Two pairs of assessors (Y.Tsuj.−Y.Tsut. and H.T.−Y.K.) assessed the eligibility of the PROSPERO records identified by the initial search. We resolved disagreements by discussion among the authors, with another author (T.A.F.) acting as an arbiter. Two pairs of assessors (Y.Tsuj.−D.P. and Y.Tsut.−Y.K.) independently extracted the following data from the relevant PROSPERO records: registration and anticipated date of completion, the number of authors, funding sources, conflicts of interests, stage of review, year of registration, and countries. We also extracted the research question of the SRs in terms of the PICO format (participant, intervention, comparator, and primary outcome) [18] from the records using the following rules: (1) the primary comparison: the intervention and comparator that were described first or as the primary in the intervention and comparator section and (2) the primary outcomes: all outcomes listed in the primary outcome section. If the authors analyzed the primary outcome more than once, we used the result that included the largest number of studies. When the primary outcome was missing in the primary outcome section of the PROSPERO, we used the one first mentioned as the primary outcome. We extracted the acceptance date from any SR published in a journal article. If the acceptance date was not available, we used the date of online publication. We chose the acceptance date rather than the publication date because the interval between acceptance and publication depends on external factors unrelated to time-lag bias—if any—based on statistical significance.

2.4. Survey

From May 4 to November 28, 2018, we asked the contacted authors of potentially eligible SRs to respond to a survey through the internet. Supplementary Files 1 and 2 show the surveys, which included 7 to 13 items and were voluntary without any incentive. For authors whose publications could not be found using PubMed or Google Scholar using the keywords for participants or intervention and/or authors' names, we asked whether or not an SR analysis had been completed. When the authors had completed the analysis but not published the SR, we sought the following information: the number of included trials in the SR; whether or not the authors had presented the SR at a scientific conference; and whether or not they had submitted the SR to a journal. To all the authors of published or completed but not published SRs, we asked the following questions: whether or not each primary outcome was statistically significant; whether the review team's involvement in any of the trials was included in the SR; whether the authors had experience in publishing an SR as a lead author before the PROSPERO registration; and whether they had a relationship with a private for-profit consulting firm for SRs.

We asked the authors to rank what they believed to be the main barriers to publishing SRs according to a classification system used in a previous study [10]. In addition, we asked if they knew of another published review addressing the same questions. All surveys were administered using SurveyMonkey (www.surveymonkey.com). To select survey recipients, we performed a random sampling of relevant SRs, stratified by whether we could find the publication or not, using a random number table. When authors did not respond to our survey, we sent repeated reminders up to 12 times. When the SRs were not eligible based on the unpublished data or when the possible respondents declined to participate, we randomly sampled another SR from the remaining pool of studies. To avoid having the survey email categorized as spam, we changed the mail source and the title several times.

We estimated that a total of 220 SRs was needed to provide approximately 90% power to detect the difference with an assumed type I error of 0.05 (two-sided) when the proportion of unpublished SRs was 50% in the protocol [17]. We attempted to repeat the random sampling of relevant SRs stratified by SRs whether we could find the publication or not until the number of eligible SRs whose authors responded to our survey reached 220 or the registry was exhausted.

2.5. Data analysis

The primary outcome data were the time for publishing SRs in journal articles, defined as the time elapsed between the registration date to the acceptance date. We defined time-lag bias as the difference in time from the registration date to the acceptance date between SRs with statistically significant results and those without statistically significant results. We described Kaplan-Meier curves for time to publication, classified by statistical significance of the review

results. We examined the association of statistical significance and time to publication using the log-rank test and Cox proportional hazard models for a univariable and a multivariable analysis, respectively. In the multivariable model, we adjusted for the number of included studies and the year of registration. The number of included studies was possibly associated with the statistical power, the importance of the topic, and the acceptance rate. The year of registration might have been associated with the novelty, the effect size of the intervention, and the acceptance rate. We tested the proportional-hazards assumption on the basis of Schoenfeld residuals after fitting the univariable and multivariable models. As a sensitivity analysis, we repeated the primary analysis, restricting SRs to those in which the authors had clearly predefined primary outcomes. We also performed a post hoc sensitivity analysis that repeated the primary analysis using time from registration to online publication instead of time from registration to acceptance.

Secondary outcomes included the proportion of SRs published in journal articles, a composite outcome of full publication or presentation at scientific conferences, and submission to any journals. We constructed a table showing the proportion of statistical significance and summarized the characteristics of included SRs classified by full publication, submission, presentation, and no dissemination. We analyzed 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 the year of registration.

Moreover, we determined as accurate the proportion of SRs that did not report the primary outcomes as defined in the protocol and the proportion of SRs for which the stage of the review process, as reported in the PROSPERO at the time of the survey. We summarized the answers of the SR authors regarding possible barriers for publishing their SRs. We expressed continuous variables as means (standardized deviations) and categorical variables as numbers with percentages (%), and considered a two-sided *P*-value smaller than 0.05 as statistically significant. We used the Stata/SE, version 14.0, software (StataCorp, College Station, TX, USA) for all analyses.

3. Results

3.1. Search results

Figure 1 shows the flow diagram: we identified a total of 1,284 records from the initial search. After the screening and handsearch for the publications, we found 333 unique SR protocols (183 eligible protocols with published results and 150 potentially eligible protocols without published results).

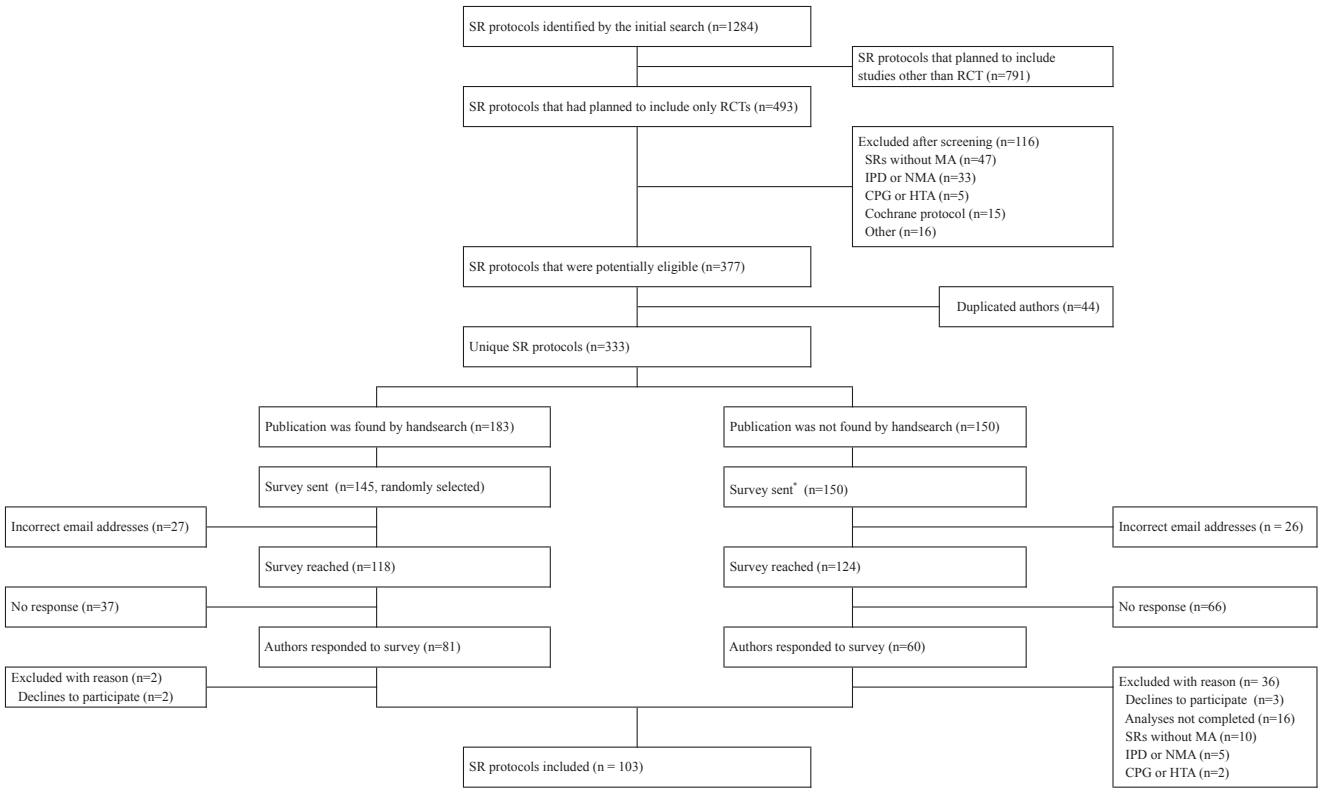

Fig. 1. Flow diagram of the present study. *We randomly selected 99 potentially eligible authors from the protocols where the publication was not found by handsearch. When the protocol was not eligible according to the authors' responses, we repeated to resample until the database was exhausted. SR, systematic review; MA, meta-analysis; IPD, individual patient data; NMA, network meta-analysis; CPG, clinical practice guideline; HTA, health technology assessment.

3.2. Survey response rate

As described in the Methods section, we had originally planned to repeat the random sampling stratified by whether we could find the publication or not when the SRs were not eligible based on the authors' responses. For SR protocols for which we could not find the publication ($n = 150$), the list was exhausted due to the exclusions ($n = 36$) or incorrect email addresses ($n = 26$) (Fig. 1). We therefore stopped sampling and included all 24 eligible SR protocols out of 60 authors who had responded. We also found that 16 of the 60 SRs had been published by the time we received the authors' reply. Among the SR protocols for which we found the publication, we sent out surveys to 145 randomly selected authors and obtained responses from 81. Excluding two authors who declined to participate, we included 79 SR protocols.

Overall, 141 (58%) of the 242 to whom we sent the invitation emails and whom we knew had received the invitation responded. Table 1 compares the protocols of those authors who responded with those authors who did not respond. There were no significant differences in terms of registration year, funding, or country. Supplementary File 3 shows the data extraction sheet of all the SR protocols to which the survey was sent and that we had confirmation that it reached.

3.3. Characteristics of included SR protocols

Of the 141 respondents, we excluded 38 (27%) because of the following reasons: 16 (11%) had not completed the analysis; 10 (7%) had performed SRs without quantitative synthesis; 5 (3%) were SRs with IPD or NMA; 2 (1%) were SRs for CPGs or HTA; and 5 (4%) declined to participate. Subsequently, we included 103 SR protocols in the present study. Supplementary File 4 shows the list of SRs whose authors agreed to participate in this study.

Ninety percent (93/103) of the included SR protocols were published before the launch of our survey on May 4, 2018. Of these 93 published SRs, we had acceptance date for 75 (81%). Sixteen percent (16/103) of the SRs for which the stage of the review process was accurate and 11% (11/103) of the included reviews did not report one or more prespecified primary outcomes. Fifty-three (51%) authors had some prior experiences in conducting SRs. The largest numbers of SRs were from China and the United Kingdom.

Table 2 tabulates these characteristics of the included SR protocols with or without statistically significant results. The proportions of unpublished SRs were 4% and 10% for SRs with and without statistically significant results, respectively. Compared to SRs with statistically significant results, those without statistically significant results tended to have smaller numbers of included studies and less often defined the timing of the outcome measurement.

Table 1. Comparison of the SR protocols whose contact authors responded and those whose authors did not respond

Characteristics	SR protocols whose authors responded to the survey ($n = 141$)	SR protocols whose authors did not respond to the survey ($n = 101$)	*P*-value[b]
Registration year			0.86
2011	12 (9)	8 (8)	
2012	25 (18)	22 (22)	
2013	63 (45)	41 (41)	
2014	41 (29)	30 (30)	
Funding	67 (48)	43 (43)	0.7
Outcome measurement timing	30 (21)	23 (23)	0.78
Country			0.056
China	20 (14)	25 (25)	
United Kingdom	22 (16)	17 (17)	
Canada	14 (10)	6 (6)	
United States	7 (5)	12 (12)	
Australia	5 (4)	5 (5)	
Multinational collaboration	11 (8)	7 (7)	
Others	62 (44)	29 (29)	
English-speaking countries[a]	63 (45)	47 (47)	0.78

Abbreviations: SR, systematic review
Values are given as number (percentage).
English countries include the United States, Canada, the United Kingdom, Ireland, Australia, and New Zealand.
[a] English-speaking countries include United States, Canada, United Kingdom, Ireland, Australia, and New Zealand.
[b] *P*-values for analysis of Pearson's chi-squared tests.

Table 2. Characteristics of included SR protocols with and without statistically significant results

Characteristics	SR protocols with SS results (n = 72)	SR protocols without SS results (n = 31)
Registration year		
2011	9 (12)	0 (0)
2012	13 (18)	6 (19)
2013	29 (40)	18 (58)
2014	21 (29)	7 (23)
RCTs included		
<10	21 (31)	15 (48)
≥10 to <20	24 (33)	9 (29)
≥20	26 (36)	7 (23)
Publication status		
Journal article	66 (92)	27 (87)
Presented but not published	3 (4)	1 (3)
Unpublished	3 (4)	3 (10)
Submission to any journal	69 (96)	29 (94)
Funding	34 (47)	14 (45)
Academic COI[a]	15 (22)	7 (23)
Prior SR experience	38 (55)	15 (50)
Outcome measurement timing	17 (24)	5 (16)
Nonreporting prespecified primary outcomes	9 (12)	2 (6)
Status in PROSPERO reflected correct publication status	12 (17)	4 (13)
Country		
China	14 (19)	2 (6)
United Kingdom	11 (15)	5 (16)
Canada	6 (8)	5 (16)
United States	3 (4)	1 (3)
Australia	3 (4)	1 (3)
Multinational collaboration	4 (6)	2 (6)
Others	31 (43)	15 (48)
English-speaking countries[b]	29 (40)	16 (52)

Abbreviations: SR, systematic review; SS, statistically significant; RCT, randomized controlled trial; COI, conflict of interests; PROSPERO, international prospective register of systematic reviews.

Values are given as number (percentage).

[a] The research team included any author involved in one of the RCTs gathered for the review.

[b] English-speaking countries include the United States, Canada, the United Kingdom, Ireland, Australia, and New Zealand.

3.4. Primary outcome

Figure 2 shows the cumulative publication rate of systematic reviews with and without statistically significant results. Median times from registration to acceptance were 1.2 years (interquartile range [IQR], 0.8 to 1.8) and 1.2 years (IQR, 0.8 to 2.3) for SRs with and without statistically significant results, respectively. Table 3 shows the association between statistically significant results and time to acceptance. An unadjusted analysis shows that statistically significant results were not associated with time to acceptance (hazard ratio [HR], 1.14; 95% confidence interval [CI], 0.73 to 1.78). The association did not change when we adjusted for year of registration and the number of RCTs included in the SR (adjusted HR, 1.36; 95% CI, 0.84 to 2.19). Both the chi-square statistics were not statistically significant, suggesting that the Cox proportional hazard assumption was satisfied (P = 0.93 for the univariable and P = 0.32 for the multivariable model). Results were similar when we used time from registration to online publication instead of time from registration to acceptance (HR, 1.10; 95% CI, 0.70 to 1.73). The sensitivity analysis restricting SRs to those in which the authors had clearly predefined primary outcomes in terms of the timing of the outcome measurement in the protocols provided an extremely wide CI that was essentially noninformative (HR, 1.57; 95% CI, 0.38 to 6.52) (Supplementary File 5).

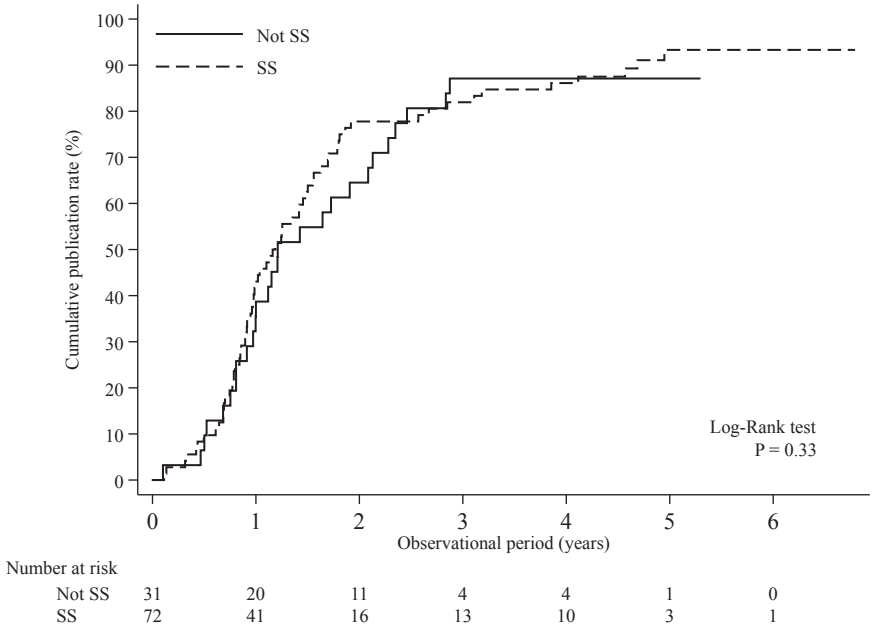

Fig. 2. Cumulative publication rate of systematic reviews with statistically significant (SS) results (solid line) and those without SS results (dashed line). Median times from registration to publication were 429 days (interquartile range [IQR], 299 to 670) days and 442 days (IQR, 295 to 857) days for systematic reviews with and without statistically significant results, respectively.

3.5. Secondary outcomes

There were no statistically significant associations between statistical significance and proportion of publication in journal articles (odds ratio [OR] 1.63; 95% CI, 0.43 to 6.23), a composite outcome of full publication, or presentation at scientific conferences (OR, 2.46; 95% CI, 0.47 to 12.95), and submission to any journals (OR, 1.59; 95% CI, 0.25 to 10.00) in the univariable analyses. The results did not change when adjusted for year of registration and the number of RCTs included (OR, 1.55; 95% CI, 0.39 to 6.13 for full publication; OR, 2.36; 95% CI, 0.42 to 13.16 for a composite outcome of full publication or presentation at scientific conferences; and OR, 1.50; 95% CI, 0.23 to 9.63 for submission to any journals).

3.6. Barriers to publishing systematic reviews

Table 4 summarizes the responses to our questionnaire about the barriers to publishing SRs. Ninety-nine (96%) of the SR authors answered the questionnaire. Fifty-two percent (51/99) of the authors answered that lack of time was a significant barrier. Other barriers included rejection by peer-reviewed journals (42% [42/99]) and duplication of a similar topic from other groups (42% [42/99]). Twenty-nine percent of the respondents (29/99) ranked

Table 3. Association between statistical significance and time to publication

Characteristics	Unadjusted HR	Adjusted HR
Review results		
Not statistically significant	Ref.	Ref.
Statistically significant	1.12 (0.71 to 1.75)	1.33 (0.82 to 2.15)
Year registered		
2011	Ref.	Ref.
2012	1.89 (0.82 to 4.39)	2.1 (0.89 to 4.93)
2013	1.35 (0.63 to 2.90)	1.43 (0.66 to 3.13)
2014	1.44 (0.64 to 3.24)	1.54 (0.68 to 3.49)
RCTs included		
<10	Ref.	Ref.
≥10 to <20	0.81 (0.49 to 1.34)	0.77 (0.46 to 1.28)
≥20	0.67 (0.41 to 1.11)	0.61 (0.36 to 1.03)

Abbreviations: HR, hazard ratio; RCT, randomized controlled trial.

Values in parentheses show 95% confidence intervals. Unadjusted model used Cox regression model. Adjusted model used multivariable Cox regression model adjusted for year registered and the number of RCTs included.

Table 4. Answers to the survey question "How do you rank the following barriers to publishing your systematic reviews" (n = 99)

Item	Significant barrier	Not significant barrier
Workplace or study funder does not want to publish	11 (11)	88 (89)
Operational issues	10 (10)	89 (90)
You are often contractually obliged not to publish the results	8 (8)	91 (92)
Lack of organizational support	31 (31)	68 (69)
Lack of funding or study funding ends before publication	34 (34)	65 (66)
Lack of time to invest in the publication process	51 (52)	48 (49)
Noninformative or nonsignificant results	29 (29)	70 (71)
Often rejected by peer-reviewed journals	42 (42)	57 (58)
Review for similar topic/interest from other research group found	42 (42)	57 (58)

Values in parentheses show percentage.

noninformative or nonsignificant results as a significant barrier.

4. Discussion

4.1. Main findings

Most SRs with completed analyses were published within 3 years after registration in the PROSPERO. Whether or not the review found a statistically significant result did not appear to affect the time to acceptance nor did statistical significance affect the authors' submissions to journals or publication in journal articles. However, around 30% of the SR authors responded that nonsignificant results could be a barrier to publication. Lack of time, rejection by journals, and duplication of similar topics were reported by authors as barriers to publication of SRs. The stage of the review process displayed in the PROSPERO rarely reflected the accurate one.

4.2. Strengths and limitations

This is the first study to investigate time-lag bias in non-Cochrane SRs. We used comprehensive searches and included the published and unpublished SR protocols using the first and largest global registry for SRs [19]. In addition to database searches, when we failed to find publications, we asked authors directly for the information. We believe our information was more accurate than other studies searching only literature databases. We further contacted the authors to obtain unpublished data, including number of included RCTs and statistical significance of SR findings. The PROSPERO registry proved instrumental in allowing us to evaluate time-lag bias in the SR field. We only included the SR analyses that were completed to exclude time-lag bias because of other causes than statistical significance of SR findings.

There were several limitations for this study. First, although we sent reminders up to 12 times, the response rate remained at 58%, suggesting that our data might not be representative of eligible SRs registered in the PROSPERO [20]. The number of included SR protocols was small and lower than the original sample size after the registry was exhausted. Thus, the CIs around our estimates were wider than would be optimal. The respondents did not appear to differ from the nonrespondents in terms of registration year of their reviews, funding, or country. In addition, our findings were based on the responses of the review authors and therefore might not necessarily be true. There were also an unexpectedly high number of exclusions due to incorrect email addresses, incomplete reviews, and SRs without meta-analyses. However, the similar median times to acceptance of the SRs with and without statistically significant results (1.2 years [IQR], 0.8 to 1.8 vs. 1.2 years [IQR, 0.8 to 2.3]) further supports the inference that time-lag bias is not an important problem in SRs.

Second, although we obtained acceptance dates from more than 80% of SRs, we needed to use the dates of online publication for studies in which acceptance dates were not available. We reasoned that the time between acceptance and online publication was a clerical process and would not be associated with statistical significance. Furthermore, we considered that the time from registration to acceptance might not reflect true time-lag bias, which is the period between obtaining the SR results and the publication. We therefore adjusted the number of RCTs included in the SRs and the year registered in the PROSPERO, because both were likely to affect the time from the registration to the completion of the analyses, and obtained similar results.

Third, this study concerned only SR protocols registered in the PROSPERO or SRs that included RCTs. The findings may not be generalizable to reviews that were planned but were not registered or reviews of studies other than RCTs. Previous studies have found that registration in the

PROSPERO was associated with better methodological quality compared with those without registration [21]. Other studies have also found that prospective registration was not associated with reporting statistical significance [22]. SRs including studies other than RCTs are at high risk of bias in terms of selection bias and are likely to find statistical significance [7,23]. Further work with the focus on these SRs may therefore yield different results.

Finally, there could be unmeasured confounding effects such as types of outcome (efficacy or harm and subjective or objective), or novelty of the findings, which may have influenced time to publication. However, because an SR typically has several outcomes, we expected most to include both efficacy or harm and subjective or objective outcomes. It was also difficult to judge the novelty of each of the SR topics at the time of registration because the PROSPERO requires SR authors to ensure that they are not unnecessarily duplicating a review that is being performed by another team or has been registered previously [15]. The methodological quality of the protocols and the publications could also be a potential confounder, but a sensitivity analysis restricting studies that adequately predefined their primary outcomes, however, provided consistent results.

4.3. Results in relation to prior studies

A previous study that showed statistical significance was not associated with time to publication in Cochrane reviews is consistent with our findings [11]. More than 70% of the SR authors in the present study answered that nonsignificant results were not a major barrier to publication, a finding also consistent with previously reported results [10]. Unlike clinical efficacy trials, SR authors might not intend to find statistical significance [2−4,6]. The primary aim to perform an SR could be to collate all empirical evidence to answer a specific research question and to rate the quality of evidence to help clinical decision making [7,24]. The awareness of the gravity of publication bias among review authors may have also prompted them to publish their products regardless of the statistical significance of their own findings. However, 30% of the respondents in our study still considered nonsignificant results to be a barrier to publication.

Duplication of similar topics was an important barrier to publishing an SR. One of the aims of the PROSPERO registry is to reduce unplanned duplication of SRs [14,25]. The Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) statement also encourages protocol registration [26]. Although SR authors could find duplication reviews using the PROSPERO, they rated duplication as a significant barrier. This might be due to the low registration rate of SRs [22]. SR authors may not optimally search for prior reviews and thus risk unnecessary duplication [27]. Although confirmation of findings of prior systematic reviews may be desirable [28], greater awareness of prospective registration, stricter standards regarding duplication in major journals, and encouragement to confirm the additional contribution of a new review could reduce the research waste of excessive duplication.

Lack of time to invest in the publication process and rejection by peer-reviewed journals were also commonly reported as barriers for publishing SRs. These results were also consistent with previous findings [10,29]. Most SR authors in this study consequently published their SRs in journal articles, but developing support tools for systematic reviewers such as title and abstract screening and data extraction using artificial intelligence may shorten the time required for the production of SRs [30].

5. Conclusion

The responses of the SR authors failed to yield evidence that time-lag bias based on statistical significance exists among SRs whose protocols are registered in the PROSPERO. SR users may therefore be somewhat reassured, at least for PROSPERO-registered reviews; definitive reassurance will require replication with a larger sample size that also includes reviews not registered in the PROSPERO. Lack of time, rejections by journals, and duplication of similar topics could be obstacles to publication of SRs, although 90% of the SR authors who registered their protocols in the PROSPERO and had completed their analyses achieved publication in journal articles.

Supplementary File 4. Sensitivity analysis restricting SRs to those in which the authors had clearly predefined primary outcomes in terms of the timing of the outcome measurement in the protocols. Note: Solid and dashed lines indicate statistically significant results and those without statistically significant results, respectively. SS, statistically significant.

CRediT authorship contribution statement

Yasushi Tsujimoto: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Project administration, Visualization, Writing - original draft. **Yusuke Tsutsumi:** Conceptualization, Data curation, Investigation, Methodology, Project administration, Writing - original draft. **Yuki Kataoka:** Conceptualization, Data curation, Investigation, Methodology, Project administration, Writing - original draft. **Hiraku Tsujimoto:** Conceptualization, Data curation, Investigation, Methodology, Writing - original draft. **Yosuke Yamamoto:** Conceptualization, Investigation, Supervision, Writing - review & editing. **Davide Papola:** Conceptualization, Data curation, Writing - original draft. **Gordon H. Guyatt:** Conceptualization, Investigation, Methodology, Project administration, Supervision, Writing - review & editing. **Shunichi Fukuhara:** Conceptualization, Supervision, Writing - review & editing. **Toshi A. Furukawa:** Conceptualization, Funding

acquisition, Investigation, Methodology, Project administration, Supervision, Writing - review & editing.

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Supplementary data

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