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BMJ Open

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

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1 **Title page**

2 **Title**

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

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Abstract

49 **Introduction**

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

56
57 **Method and analysis**

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

67
68 **Ethics and dissemination**

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

73

74 **Trial registration number: UMIN000028325**

75

76 **Strengths and limitations of this study**

- 77 • This is the first study to contact the authors of unpublished systematic reviews (SRs)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

88

89 **INTRODUCTION**

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

95 Publication bias occurs when the choice of authors' write-up and submission or editors'
96 acceptance for publication is influenced by the direction or strength of the study findings
97 [6]. When this happens, findings of published studies will be systematically different
98 from those of unpublished studies and hence from the underlying truth (Figure 1) [7].

99 Time lag bias is one aspect of publication bias which arises when the speed of publication
100 depends on the direction and nature of the randomized clinical trial (RCT) results [2, 7, 8].

101 In RCTs, trials without statistical significant results take a longer time before publication
102 than trials with statistical significant results (Figure 1) [4]. One recent study found that
103 the main barrier for publication was at the stage of authors rather than editors or reviewers
104 [7, 9]. With respect to time lag in particular, one can characterize the phenomenon as
105 either delay due to non-significant results, or expedited submission and publication due to
106 significant results.

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

113 facilitator for publishing SRs – in other words authors are more likely, faced with other
114 pressures, to take the time to complete and submit their review when they have positive
115 results to report. Other studies suggested that statistical significant results were not
116 associated with time to publication of Cochrane reviews [12]. On the other hand,
117 non-Cochrane SRs were likely to report statistical significance findings and positive
118 conclusions [13]. We recently reported more than 30% of non-Cochrane SRs registered
119 in the international prospective register of systematic reviews (PROSPERO) were not
120 published after at least 65 months of registration [14]. These results indicate that
121 publication bias and time lag bias among non-Cochrane SRs may well exist.
122 This study therefore aims to investigate whether or not publication bias and time lag bias
123 in SRs based on statistical significance exist. We will also evaluate other factors
124 associated with time to publication.

125

126 **OBJECTIVES**

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

130

131 **METHODS AND ANALYSIS**

132 Inclusion and exclusion criteria

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

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

143 Search method

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

153 Study selection

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

158 Data extraction

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

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5 161 Registration and anticipated date of completion, the number of authors, funding sources,
6
7 162 conflicts of interests (COIs), stage of review, year of registration, and countries that the
8
9 163 study has been conducted. We will define the primary review question of the SR in terms
10
11 164 of participant, intervention, comparator, and primary outcome. As the review may
12
13 165 provide several comparisons for the same class of interventions and comparators, we will
14
15 166 define the primary comparison as the intervention and comparator that are described as
16
17 167 the primary or the first one in the intervention and comparator section in the PROSPERO
18
19 168 record, and the primary outcomes as all outcomes listed in the primary outcome section of
20
21 169 PROSPERO. Should the primary outcome be missing in the primary outcome section of
22
23 170 PROSPERO, we will define the one mentioned first as the primary outcome. For SRs
24
25 171 published in a journal article, we will extract the date of acceptance. If acceptance date is
26
27 172 not available, we will use the publication date for SRs published in open access journals,
28
29 173 and contact the authors or the editorial office for SRs published in other journals.
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176 Survey

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

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

193
194 Sample size

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

202
203 Data analysis

204 Primary analyses

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

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

216

217 Secondary analyses

218 Secondary outcomes will include (iii) a composite outcome of full-publication or
219 presentation at scientific conferences, and (iv) submission to any journals. We will
220 describe the proportion of statistical significance and summarize the characteristics of
221 included SRs classified by full publication, submission, presentation, and no
222 dissemination. We will analyse the association between statistically significant findings
223 and the secondary outcomes using the same univariate logistic regression, multivariate
224 logistic regression, Kaplan-Meier curves and Cox regression as the primary outcomes.
225 When there is a statistically significant association between statistically significant
226 findings and the proportion or time to publication, we will explore the associated factors.
227 We will examine the association of the proportion or time to publication with academic or
228 financial COI, experience of SR publication, country of contact author's affiliation
229 (English speaking or not), or multinational collaboration using Log-rank test.
230 Additionally, we will use Cox proportional hazard model to explore the strongest factors
231 associated with SR publication. We will summarize proportion of SRs that have not
232 reported the primary outcomes as defined in the protocol among published SRs. We will

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

235

236 Sensitivity analysis

237 We will conduct the following pre-specified sensitivity analysis;

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

240

241 **ETHICS AND DISSEMINATION**

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

248

249 **DISCUSSION**

250 SRs with adequate quality have potentials to alter the daily clinical practice, and are
251 useful resources in developing clinical practice guidelines and policies. Publication bias
252 and time lag bias can be a strong barrier to research transparency and integrity. Before the
253 launch of PROSPERO, we did not have a tool to find SR protocols that remained
254 unpublished. After six years from its launch, the registry will enable us to evaluate
255 publication bias and time lag bias in the SR field, as was the case of clinical trial registries
256 [7]. This is the first study to contact the authors of unpublished SRs and investigate the

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

264 There are several expected limitations for this study. First, the generalizability will be
265 limited because the analyses investigating the biases include only those who registered
266 the protocol in the PROSPERO and respond to our survey. In order to increase the
267 response rate, we will remind the contact authors up to 10 times for every week if they do
268 not respond to our survey. Secondly, the time to publication may not reflect true time lag
269 bias that is the period between the initiation of the SR and its publication because
270 protocols may be registered after their analyses. The PROSPERO prohibits registration of
271 completed reviews but some may nonetheless register after the completion of the analysis
272 [16]. Because SRs that registered after their completion are more likely to have
273 statistically significant findings and may be published earlier, if there are many such
274 protocols, our hypothesized association may be overestimated. Thirdly, there can be
275 unmeasurable confounding such as the methodological quality of the protocol. We will
276 therefore perform a sensitivity analysis to restrict studies that adequately pre-defined
277 their primary outcomes.

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

281

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284 managing the PROSPERO

285

286 Contributions

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

291

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295

296 Competing interests

297 TAF has received lecture fees from Eli Lilly, Janssen, Meiji, MSD, Otsuka,
298 Pfizer and Tanabe-Mitsubishi, and consultancy fees from Takeda Science
299 Foundation. He has received research support from Mochida and
300 Tanabe-Mitsubishi. All the other authors report no competing interests to
301 declare.

302

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305 cohort study of clinical research projects. *Bmj*. 1997;315(7109):640-5.
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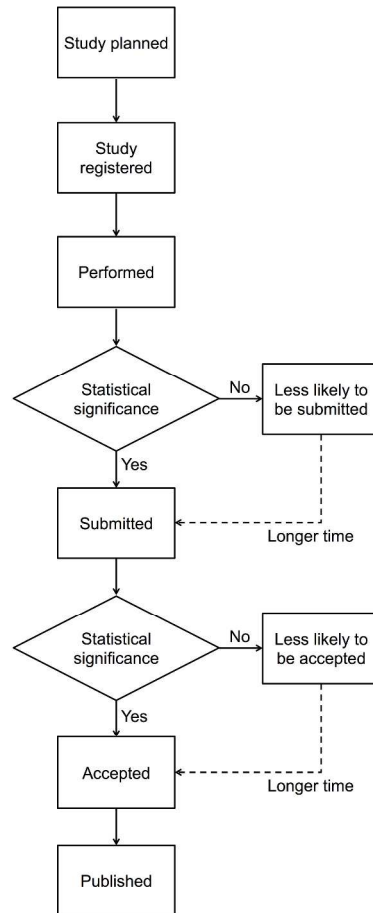


Figure 1. Concept of the present study
Study with statistical significant findings may be more likely to be submitted, accepted, and published (publication bias) and published earlier (time lag bias).

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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)

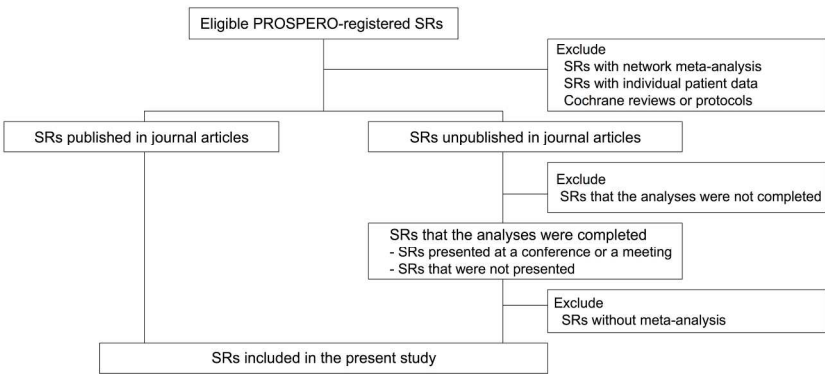


Figure 2. Expected flow diagram of the present study
PROSPERO = the international prospective register of systematic reviews, SR = systematic review, IPD = individual patient data

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49 **Abstract**

50 **Introduction**

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

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

68

69 **Ethics and dissemination**

70 Ethics approval will be obtained from the Ethical Committee of the Kyoto University
71 Graduate School of Medicine. This protocol has been registered in the University hospital
72 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

89 **INTRODUCTION**

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

95 Publication bias occurs when the authors' decision to write and submit the results or
96 editors' acceptance for publication is influenced by the direction or strength of the study
97 findings [6]. When this happens, findings of published studies will be systematically
98 different from those of unpublished studies and hence from the underlying truth (Figure
99 1) [7].

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

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

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5 113 Cochrane and non-Cochrane reviews [12, 13]. A survey among first or corresponding
6
7 114 authors of SRs indicated that unpublished SRs exist [14]. The authors reported common
8
9 115 reasons for not publishing SRs including lack of time and the manuscript being rejected
10
11 116 by journals. Statistical significance was not reported as being a major barrier or reason for
12
13 117 not publishing, but 65% of respondents reported significant results as a significant
14
15 118 facilitator for publishing SRs – in other words authors are more likely, faced with other
16
17 119 pressures, to take the time to complete and submit their review when they have positive
18
19 120 results to report. Moreover, non-Cochrane SRs were likely to report statistical
20
21 121 significance findings and positive conclusions [13]. We recently reported more than 30%
22
23 122 of non-Cochrane SRs registered in the international prospective register of systematic
24
25 123 reviews (PROSPERO) were not published after at least 50 months of registration [15].
26
27 124 These results indicate that time lag bias and publication bias among non-Cochrane SRs
28
29 125 may well exist.
30
31 126 This study therefore aims to investigate whether or not time lag bias and publication bias
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33 127 in SRs based on statistical significance exist. We will also evaluate other factors
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35 128 associated with time to publication.
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43 **OBJECTIVES**

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45 131 We aim to evaluate the association between statistical significance of meta-analysis result
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47 132 and publication status using a number of criteria (full publication in a journal article,
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49 133 submission to any journals, presentation of an abstract at a meeting) among SRs. We also
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51 134 aim to examine other factors of possible influence and publication of SRs.
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56 **METHODS AND ANALYSIS**

137 Inclusion and exclusion criteria

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

148 Search method

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

159 Study selection

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

161 identified by the initial search will be divided into two sets and two pairs of assessors
162 (YT_{suj}, YT_{sut}, HT, and YK) will assess the eligibility for each set separately. We will
163 resolve disagreements by discussion between the authors, with another author (TAF)
164 acting as an arbiter.

165

166 Data extraction

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

185 use the publication date for SRs published in open access journals, and the date of online
186 publication ahead of print for SRs published in other journals. We will contact the authors
187 or the editorial office if the relevant date is missing.
188
189
190 Survey
191 For potentially eligible SRs, we will contact the authors listed in the “Contact details for
192 further information” of the PROSPERO records and will ask them to respond to a survey
193 through the Internet. Through the survey, all contact authors of potentially eligible
194 unpublished SRs will be asked whether or not the SR analysis has been completed.
195 Additionally, all contact authors of published or completed but not published SRs will be
196 asked the following information; whether or not each of the primary outcomes in the
197 primary comparison (as defined by a decision rule described in Data extraction section
198 above) was statistically significant; the review team’s involvement in any of the trials
199 included in the SR; the author’s experience to publish an SR as a lead author before the
200 PROPERO registration; relationship with a private for-profit consulting firm for SRs; and
201 main barriers to publish the SR according to a classification used in a previous study [14].
202 In addition, we will ask if someone has published a review addressing the same
203 question. If the authors have completed the analysis but not published it, the following
204 information will be sought; the number of included trials in the SR; whether or not they
205 have presented the SR at a scientific conference; and whether or not they have submitted
206 the SR to any journals. All survey will be administered using Google Form
207 (<https://www.google.com/intl/en/forms/about>). We will send a reminder along with the
208 Google form link one week after the initial contact. If the authors have not responded by

209 that time, we will repeat this process twice.

210

211 Sample size

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

223

224 Data analysis

225 Primary analyses

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

233 of included studies possibly associates with the importance of the topic, and the increase
234 of statistical power. The year of registration may associate with the effect size of the
235 intervention, and the acceptance rate of SRs.
236
237 Secondary analyses
238 Secondary outcomes will include (ii) proportion of SR published in journal articles, (iii) a
239 composite outcome of full-publication or presentation at scientific conferences, and (iv)
240 submission to any journals. We will describe a table showing the proportion of statistical
241 significance and summarize the characteristics of included SRs classified by full
242 publication, submission, presentation, and no dissemination. We will analyse the
243 association between statistically significant findings and the secondary outcomes using
244 univariable logistic regression, and multivariable logistic regression to adjust for the
245 number of included studies and year of registration.
246 When there is a statistically significant association between statistically significant
247 findings and time to publication, we will explore the predictors of time to publication
248 other than statistical significance, number of included studies, and year of publication.
249 First, we will examine the association of the proportion or time to publication with
250 academic or financial COI, experience of SR publication, country of contact author's
251 affiliation (English speaking or not), or multinational collaboration using Log-rank test.
252 Then, we will use Cox proportional hazard model to explore the influence of these factors
253 on the association between statistical significance and time to publication. We will
254 summarize proportion of SRs that have not reported the primary outcomes as defined in
255 the protocol among published SRs. We will describe whether or not the PROSPERO
256 status reflect the true publication status and will summarize the barriers for completed

257 SRs to publish.

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

262
263 Sensitivity analysis

264 We will conduct the following pre-specified sensitivity analysis;

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

268 ETHICS AND DISSEMINATION

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

277 DISCUSSION

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

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5 281 launch of PROSPERO, it was difficult to find SR protocols that remained unpublished.
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7 282 After six years from its launch, the registry will enable us to evaluate publication bias and
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9 283 time lag bias in the SR field, as was the case of clinical trial registries [7]. This is the first
10
11 284 study to contact the authors of unpublished SRs and investigate the existence and the
12
13 285 magnitude of these biases. We recently suggested that protocol registration was not
14
15 286 associated with reporting of statistical significance [16]. The factors associated with
16
17 287 publication or time to publication of SRs will inform potential preventive measures for
18
19 288 these biases. We also aim to describe the publication rate of registered protocols and the
20
21 289 proportion of published SRs that have not reported primary outcomes as defined in the
22
23 290 protocol, and check whether the PROSPERO status reflects the true publication status.
24
25 291 There are several expected limitations for this study. First, the generalizability will be
26
27 292 limited because the analyses investigating the biases include only those who registered
28
29 293 the protocol in the PROSPERO and respond to our survey. In order to increase the
30
31 294 response rate, we will remind the contact authors up to 2 times for every week if they do
32
33 295 not respond to our survey. Secondly, the time to publication may not reflect true time lag
34
35 296 bias that is the period between the initiation of the SR and its publication because
36
37 297 protocols may be registered after their analyses. The PROSPERO prohibits registration of
38
39 298 completed reviews but some may nonetheless register after the completion of the analysis
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41 299 [17]. Because SRs that registered after their completion are more likely to have
42
43 300 statistically significant findings and may be published earlier, if there are many such
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45 301 protocols, our hypothesized association may be overestimated. Thirdly, there can be
46
47 302 unmeasurable confounding such as the methodological quality of the protocol. We will
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49 303 therefore perform a sensitivity analysis to restrict studies that adequately pre-defined
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51 304 their primary outcomes. Finally, unlike clinical trials, the authors may not intend to find
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305 statistical significance in the realm of SRs. This may bias the association the between
306 statistical significance and publication towards null.

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

310

311 Acknowledgement

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

314

315 Contributions

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

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

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

327

328

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331 Research) Grant Number 17K19808 to TAF. The funder plays no role in developing the
332 protocol.

334 Competing interests

335 TAF has received lecture fees from Eli Lilly, Janssen, Meiji, MSD, Otsuka,
336 Pfizer and Tanabe-Mitsubishi, and consultancy fees from Takeda Science
337 Foundation. He has received research support from Mochida and
338 Tanabe-Mitsubishi. All the other authors report no competing interests to
339 declare.

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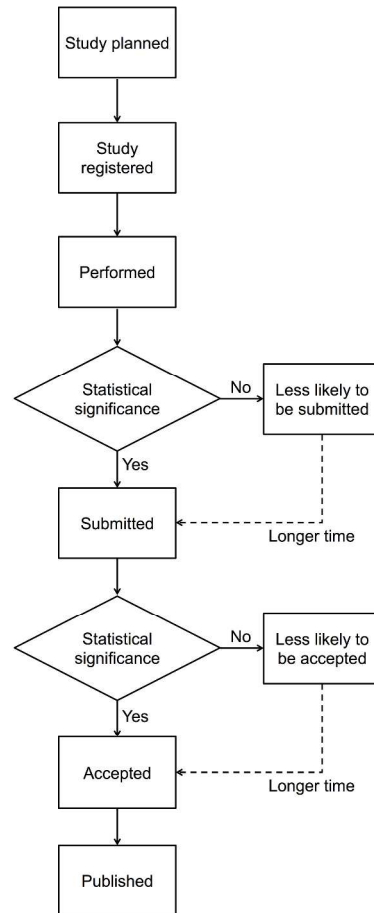


Figure 1. Concept of the present study
Study with statistical significant findings may be more likely to be submitted, accepted, and published (publication bias) and published earlier (time lag bias).

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).

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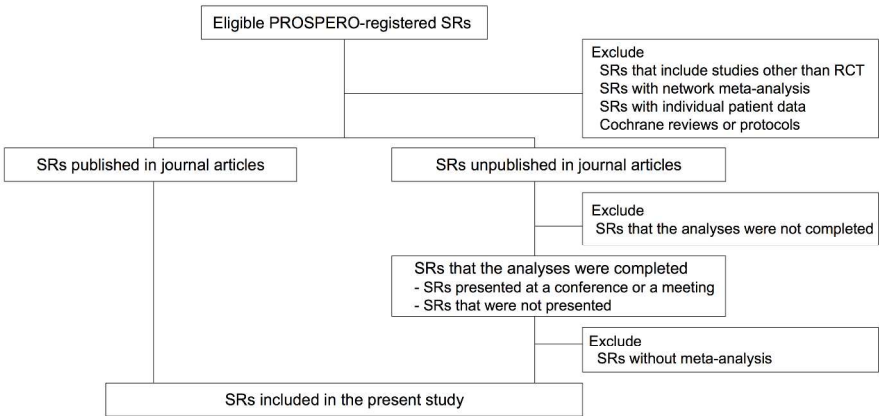


Figure 2. Expected flow diagram of the present study
PROSPERO = the international prospective register of systematic reviews, SR = systematic review,
RCT = randomised controlled trial

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 τ) 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.**

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

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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

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1 1 **Title page**

2 2 **Title**

3 3 Association between statistical significance and time to publication among systematic
4 4 reviews: a study protocol for a meta-epidemiological investigation

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45 43 **Word count: 2506**
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49 **Abstract**

50 **Introduction**

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

57

58 **Method and analysis**

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

68

69 **Ethics and dissemination**

70 Ethics approval will be obtained from the Ethical Committee of the Kyoto University
71 Graduate School of Medicine. This protocol has been registered in the University hospital
72 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

89 **INTRODUCTION**

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

95 Publication bias occurs when the authors' decision to write and submit the results or
96 editors' acceptance for publication is influenced by the direction or strength of the study
97 findings [6]. When this happens, findings of published studies will be systematically
98 different from those of unpublished studies and hence from the underlying truth (Figure
99 1) [7].

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

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

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5 113 Cochrane and non-Cochrane reviews [12, 13]. A survey among first or corresponding
6
7 114 authors of SRs indicated that unpublished SRs exist [14]. The authors reported common
8
9 115 reasons for not publishing SRs including lack of time and the manuscript being rejected
10
11 116 by journals. Statistical significance was not reported as being a major barrier or reason for
12
13 117 not publishing, but 65% of respondents reported significant results as a significant
14
15 118 facilitator for publishing SRs – in other words authors are more likely, faced with other
16
17 119 pressures, to take the time to complete and submit their review when they have positive
18
19 120 results to report. Moreover, non-Cochrane SRs were likely to report statistical
20
21 121 significance findings and positive conclusions [13]. We recently reported more than 30%
22
23 122 of non-Cochrane SRs registered in the international prospective register of systematic
24
25 123 reviews (PROSPERO) were not published after at least 50 months of registration [15].
26
27 124 These results indicate that time lag bias and publication bias among non-Cochrane SRs
28
29 125 may well exist.
30
31 126 This study therefore aims to investigate whether or not time lag bias and publication bias
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33 127 in SRs based on statistical significance exist. We will also evaluate other factors
34
35 128 associated with time to publication.
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43 **OBJECTIVES**

44
45 131 We aim to evaluate the association between statistical significance of meta-analysis result
46
47 132 and publication status using a number of criteria (full publication in a journal article,
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49 133 submission to any journals, presentation of an abstract at a meeting) among SRs. We also
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51 134 aim to examine other factors of possible influence and publication of SRs.
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56 **METHODS AND ANALYSIS**

137 Inclusion and exclusion criteria

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

148 Search method

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

159 Study selection

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

161 identified by the initial search will be divided into two subsamples of 250, and two pairs
162 of assessors (YT_{suj} - YT_{sut}, and HT - YK) will assess the eligibility for each set
163 separately. We will resolve disagreements by discussion between the authors, with
164 another author (TAF) acting as an arbiter.

165

166 Data extraction

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

185 use the publication date for SRs published in open access journals, and the date of online
186 publication ahead of print for SRs published in other journals. We will contact the authors
187 or the editorial office if the relevant date is missing.
188
189
190 Survey
191 For potentially eligible SRs, we will contact the authors listed in the “Contact details for
192 further information” of the PROSPERO records and will ask them to respond to a survey
193 through the Internet. Through the survey, all contact authors of potentially eligible
194 unpublished SRs will be asked whether or not the SR analysis has been completed.
195 Additionally, all contact authors of published or completed but not published SRs will be
196 asked the following information; whether or not each of the primary outcomes in the
197 primary comparison (as defined by a decision rule described in Data extraction section
198 above) was statistically significant; the review team’s involvement in any of the trials
199 included in the SR; the author’s experience to publish an SR as a lead author before the
200 PROPERO registration; relationship with a private for-profit consulting firm for SRs; and
201 main barriers to publish the SR according to a classification used in a previous study [14].
202 In addition, we will ask if someone has published a review addressing the same
203 question. If the authors have completed the analysis but not published it, the following
204 information will be sought; the number of included trials in the SR; whether or not they
205 have presented the SR at a scientific conference; and whether or not they have submitted
206 the SR to any journals. All survey will be administered using Google Form
207 (<https://www.google.com/intl/en/forms/about>). We will send a reminder along with the
208 Google form link one week after the initial contact. If the authors have not responded by

209 that time, we will repeat this process twice.

210

211 Sample size

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

223

224 Data analysis

225 Primary analyses

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

233 of included studies possibly associates with the importance of the topic, and the increase
234 of statistical power. The year of registration may associate with the effect size of the
235 intervention, and the acceptance rate of SRs.
236
237 Secondary analyses
238 Secondary outcomes will include (ii) proportion of SR published in journal articles, (iii) a
239 composite outcome of full-publication or presentation at scientific conferences, and (iv)
240 submission to any journals. We will describe a table showing the proportion of statistical
241 significance and summarize the characteristics of included SRs classified by full
242 publication, submission, presentation, and no dissemination. We will analyse the
243 association between statistically significant findings and the secondary outcomes using
244 univariable logistic regression, and multivariable logistic regression to adjust for the
245 number of included studies and year of registration.
246 When there is a statistically significant association between statistically significant
247 findings and time to publication, we will explore the predictors of time to publication
248 other than statistical significance, number of included studies, and year of publication.
249 First, we will examine the association of the proportion or time to publication with
250 academic or financial COI, experience of SR publication, country of contact author's
251 affiliation (English speaking or not), or multinational collaboration using Log-rank test.
252 Then, we will use Cox proportional hazard model to explore the influence of these factors
253 on the association between statistical significance and time to publication. We will
254 summarize proportion of SRs that have not reported the primary outcomes as defined in
255 the protocol among published SRs. We will describe whether or not the PROSPERO
256 status reflect the true publication status and will summarize the barriers for completed

257 SRs to publish.

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

262
263 Sensitivity analysis

264 We will conduct the following pre-specified sensitivity analysis;

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

268 ETHICS AND DISSEMINATION

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

277 DISCUSSION

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

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5 281 launch of PROSPERO, it was difficult to find SR protocols that remained unpublished.
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7 282 After six years from its launch, the registry will enable us to evaluate publication bias and
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9 283 time lag bias in the SR field, as was the case of clinical trial registries [7]. This is the first
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11 284 study to contact the authors of unpublished SRs and investigate the existence and the
12
13 285 magnitude of these biases. We recently suggested that protocol registration was not
14
15 286 associated with reporting of statistical significance [16]. The factors associated with
16
17 287 publication or time to publication of SRs will inform potential preventive measures for
18
19 288 these biases. We also aim to describe the publication rate of registered protocols and the
20
21 289 proportion of published SRs that have not reported primary outcomes as defined in the
22
23 290 protocol, and check whether the PROSPERO status reflects the true publication status.
24
25 291 There are several expected limitations for this study. First, the generalizability will be
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27 292 limited because the analyses investigating the biases include only those who registered
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29 293 the protocol in the PROSPERO and respond to our survey. In order to increase the
30
31 294 response rate, we will remind the contact authors up to 2 times for every week if they do
32
33 295 not respond to our survey. Secondly, the time to publication may not reflect true time lag
34
35 296 bias that is the period between the initiation of the SR and its publication because
36
37 297 protocols may be registered after their analyses. The PROSPERO prohibits registration of
38
39 298 completed reviews but some may nonetheless register after the completion of the analysis
40
41 299 [17]. Because SRs that registered after their completion are more likely to have
42
43 300 statistically significant findings and may be published earlier, if there are many such
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45 301 protocols, our hypothesized association may be overestimated. Thirdly, there can be
46
47 302 unmeasurable confounding such as the methodological quality of the protocol. We will
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49 303 therefore perform a sensitivity analysis to restrict studies that adequately pre-defined
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51 304 their primary outcomes. Fourth, the accuracy of PROSPERO filters is unknown, but the
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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 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

YTsuji and YTsut contributed equally to this work. YTsuji, Ytsut, HT, YK, YY, DP, GHG, SF, and TAF contributed to the conception and design of the research. YTsuji 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:

YTsuji, Ytsut, HT, YK, and DP will screen the relevant records of the PROSPERO, and extract data. YTsuji, Ytsut, HT, YK, DP, GHG, and TAF will contact the authors for additional information. YTsuji, Ytsut, YY, and TAF will conduct the data analysis without blinding of the data. YTsuji, 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.

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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.

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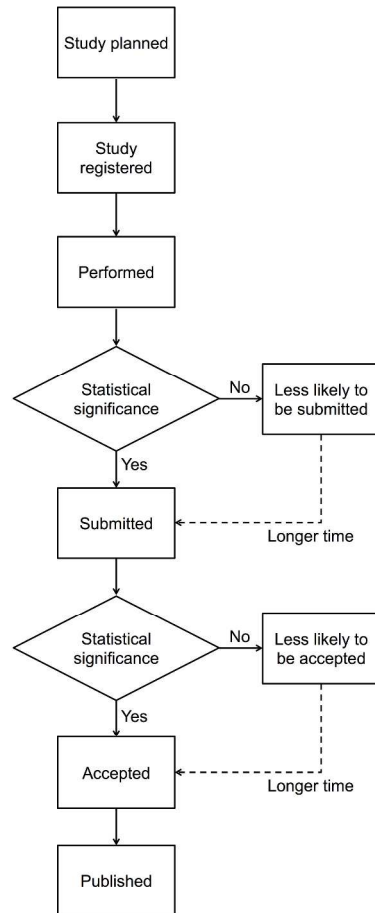


Figure 1. Concept of the present study
Study with statistical significant findings may be more likely to be submitted, accepted, and published (publication bias) and published earlier (time lag bias).

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Study with statistical significant findings may be more likely to be submitted, accepted, and published (publication bias) and published earlier (time lag bias).

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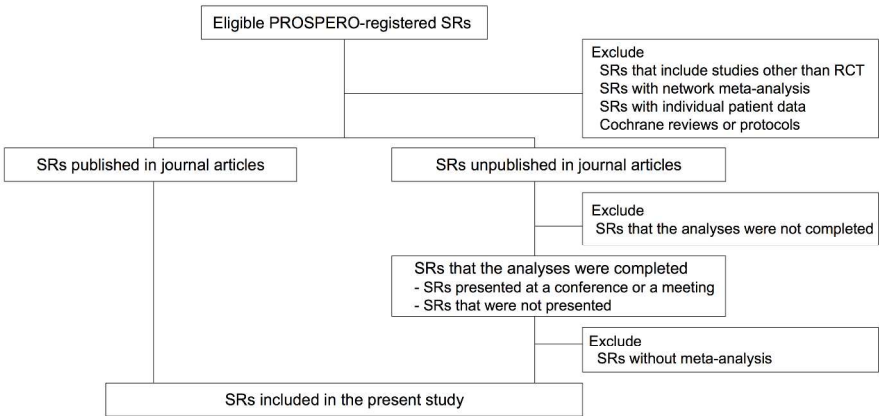


Figure 2. Expected flow diagram of the present study
PROSPERO = the international prospective register of systematic reviews, SR = systematic review,
RCT = randomised controlled trial

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

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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 τ) 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.**

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