

REVIEW

Around ten percent of most recent Cochrane reviews included outcomes in their literature search strategy and were associated with potentially exaggerated results: A research-on-research study

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Abstract

Objectives: To assess the proportion of the recent Cochrane reviews that included outcomes in their literature search strategy, how often they acknowledged these limitations, and how qualitatively different the results of outcomes included and not included in the search strategy were.

Design and Setting: We identified all the Cochrane reviews of the interventions published in 2020 that used a search strategy connecting outcome terms with “AND.” Reviews were defined as acknowledging the limitations of searching for outcomes if they mentioned them in the discussion. We compared the characteristics of outcomes included and not included in the search strategy.

Results: Of the 523 Cochrane reviews published in 2020, 51 (9.8%) included outcomes in their search strategy. Only one review acknowledged it as a limitation. Forty-seven (92%) assessed outcomes not included in the search strategy. Outcomes included in the search strategies tended to include a larger number of studies and show their effects in favor of the intervention.

Conclusions: Around ten percent of the recent Cochrane reviews included outcomes in their search, which may have resulted in more outcomes significantly in favor of the intervention. Reviewers should be more explicit in acknowledging the potential implications of searching for outcomes. © 2021 The Authors. Published by Elsevier Inc. This is an open access article under the CC BY license (<http://creativecommons.org/licenses/by/4.0/>)

Keywords: Systematic review; meta-analysis; search strategy; selective outcome reporting; publication bias; meta-epidemiology

Conflict of Interest: Dr Furukawa reports grants and personal fees from Mitsubishi-Tanabe, personal fees from MSD, and grants and personal fees from Shionogi outside the submitted work. In addition, Dr Furukawa has a patent (2020-548587) concerning smartphone Cognitive Behavior Therapy applications pending and intellectual properties for Kokoro-app licensed to Mitsubishi-Tanabe. The other authors have no conflicts of interest to declare.

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What is new?

Key findings

- We found that approximately 10% of recent Cochrane reviews on interventions included outcomes in their literature search strategies.
- Authors who have conducted the above types of reviews have not tended to acknowledge the limitations of searching for outcomes in discussions or the Grading of Recommendations Assessment, Development and Evaluation (GRADE) assessment of the certainty of evidence.
- Ninety-two percent of the reviews searching for outcomes assessed outcomes not included in the search strategy.
- Outcomes that were used in search strategies significantly differed from those that were not, particularly regarding the number of studies, direction of the effect, statistical significance, and certainty of evidence.

What this study adds to what was known

- Although it is widely recommended not to search for outcomes when conducting systematic reviews, we found some cases of recent Cochrane reviews included terms about outcomes in the search strategy without indicating any limitations

What is the implication and what should change now?

- Systematic reviewers who decided to include terms about outcomes in the search strategy should acknowledge the limitations of searching for outcomes.

1. Introduction

Systematic reviews seek to collate all the available evidence that is relevant to a specific research question. As these efforts often result in critical information that is considered when making decisions about health and social care [1,2], it is important to implement rigorous search strategies [3]. In general, the search strategies used to retrieve articles from bibliographic databases, such as MEDLINE or EMBASE are structured to consist of the 3 following sets of terms: (i) the study population, (ii) the evaluated interventions, and (iii) the items relevant to the type of study design [2]. Importantly, research has shown that the practice of including the outcome terms as part of the search strategy returns fewer relevant studies [4]. This fact may be due to selective outcome reporting and/or publication bias, where only the positive results are likely to be reported [5–10]. Moreover, these types of systematic reviews may also assess other outcomes than those that they

had used in the search strategy. Important evidence may be overlooked when researchers focus on collecting articles that contain certain outcomes in the title or abstract but then assess outcomes that were not included in the search strategy. This practice may especially miss relevant studies that did not report the results in the abstract due to their non-significance [11].

To the best of our knowledge, no previous studies have investigated this topic within the relevant literature. As such, we assessed the recent Cochrane reviews to determine: i) the proportion that included outcomes in their search terms, ii) how often the limitations of this practice were acknowledged, iii) the proportion of the Cochrane reviews that assessed outcomes other than those implemented in the search strategy, and iv) how outcomes that were not included in search strategies differed from those that were included.

2. Methods

This cross-sectional study was conducted in accordance with previously established guidelines for reporting meta-epidemiological methodology research [12]. The study protocol was published with protocols.io [13].

2.1. Eligibility criteria

We included all the Cochrane reviews on the interventions published in 2020 that searched for the specific outcome terms in the MEDLINE search strategy by combining them with the terms related to the participants or interventions via “AND.” We included reviews irrespective of the version (new or updated). Table 1 shows an example of an eligible review. We excluded the reviews that did not find studies that were eligible for inclusion, reviews with network meta-analyses, and reviews without a Summary of Findings (SoF) table. We restricted the reviews to those with a SoF table because the table includes evaluations of certainty of evidence according to GRADE, in which an evaluation of publication bias was mandatory, and we were thus able to examine in all such reviews if the reviewers had considered the possibilities of publication bias in their review.

2.2. Search strategy and study selection

On January 26, 2021, we searched the Cochrane Database of Systematic Reviews by using a filter aimed at returning reviews on interventions from January 1 to December 31, 2020. To identify whether a given Cochrane review included an SoF table and MEDLINE search strategy in the appendix, one investigator scraped these elements from the Cochrane library’s website for each review using Python. This was the selenium package version 3.141.0 [14]. Thereafter, two investigators independently confirmed these for accuracy based on the full respective texts. For

Table 1. An example of a Cochrane review which included terms related to outcomes in its literature search strategy

Title	Outcomes	Search strategy (excerpt containing the outcome terms)
Interventions for preventing silent cerebral infarcts in people with sickle cell disease [21]	• Proportion of participants developing new or progressive SCI lesions on MRI • All-cause mortality • Serious adverse events (SAEs) associated with different therapies or SCD • Clinical stroke (according to short-, medium-, and long-term outcomes) • Cognitive function as assessed by validated scales (such as Wechsler scales) from baseline and at various time intervals as reported in trials (at least 6 mo) • Quality of life as assessed by validated scales (at least 6 mo) • Any adverse events associated with different therapies	7. exp Cerebral Infarction/ 8. Brain Infarction/ 9. Stroke/ 10. Stroke, Lacunar/ 11. ((ischemic or ischaemic or cerebrovascular) adj2 (event* or injur* or complication*)).tw,kf. 12. ((MRI or magnetic resonance imaging or neuroimaging or white matter) adj3 abnormal*).tw,kf. 13. (cerebral vasculopath* or cerebrovascular accident* or cerebral vascular accident*).tw,kf. 14. ((cerebral or cerebellar or cerebrovascular or choroidal or hemisphere* or cortical or subcortical or brain*) adj3 (infarct* or ischemi* or ischaemi* or stroke*)).tw,kf. 15. ((asymptomatic* or silent* or nonsymptomatic* or unsymptomatic* or non-symptomatic* or quiet* or symptomfree or symptom-free or symptomless or symptom-less or occult or "free of symptom" or "free of symptoms" or subclinical* or covert* or incomplete*) adj5 (infarct* or ischemi* or ischaemi* or stroke*)).tw,kf. 16. or/7-15

Abbreviations: SCI, silent cerebral infarcts; MRI, magnetic resonance imaging; SAE, serious adverse events; SCD, sickle cell disease

the reviews with SoF tables and MEDLINE search strategies, two investigators independently screened the full texts and assessed them for their eligibility using the criteria mentioned above. The investigators had various pertinent backgrounds, including those in internal medicine (YTsut and YK), nephrology (YT), general surgery (YTsut), emergency care (YTsut), pulmonology (YK), psychiatry (MB and TAF), and epidemiology (all authors). Any discrepancies were resolved through discussions. If this failed, then a third investigator acted as an arbiter.

2.3. Study outcomes

The main outcomes of interest were as follows: i) The proportion of the Cochrane reviews that included outcomes in their MEDLINE search strategies as necessary terms out of all the Cochrane reviews in 2020, ii) The proportion of the Cochrane reviews, where the researchers acknowledged the limitations associated with searching for outcomes, and iii) The proportion of the Cochrane reviews that searched for outcomes but assessed outcomes other than those in the MEDLINE search strategy. For the outcomes ii) and iii), the denominator was the number of Cochrane reviews that included terms related to outcomes in their search strategy.

The reviews that acknowledged the limitations of searching for outcomes were defined as those that mentioned this issue in the discussion section or thus downgraded the certainty of the evidence in the publication bias domain of the Grading of Recommendations Assessment, Development and Evaluation (GRADE).

2.4. Data extraction

Two investigators extracted the following data independently and in duplicates: acknowledgments of the limita-

tions of including outcomes in the search strategy, included types of study designs, whether the outcomes implied in the title of the Cochrane review related to prevention or adverse effects, the numbers of articles screened, the numbers of included studies, the numbers of excluded studies with reasons for wrong outcomes, involvement of information specialists from the Cochrane review group, and the numbers of outcomes in the “Types of Outcomes” section, separately for those in the search strategy and those not. Additionally, Cochrane review groups and the number of previous Cochrane reviews written by the respective first authors were extracted from the Cochrane Library search. As a post-hoc investigation in response to the peer-reviewer’s comment, we extracted whether any new outcome was added that was not found in the protocol or the previous version of the review, whether such outcome was included in the search strategy, whether both MeSH terms and free words related to the outcomes were searched in each review.

To investigate the differences between the reviews that included outcomes in their search strategies and those that did not, we used the top seven outcomes listed in the first SoF table in each Cochrane review. Here, the Cochrane reviews provided key information concerning the magnitudes of the relative and absolute effects of the examined interventions, the amounts of available evidence, and certainty of the available evidence for up to seven outcomes in their SoF tables [2]. Regarding the outcomes listed in these SoF tables, we abstracted whether they were included in the search strategies as outcome terms. We also summarized the number of studies reporting them, their statistical significance, the direction of the effects (interventions favored or not favored), and the GRADE certainty of evidence.

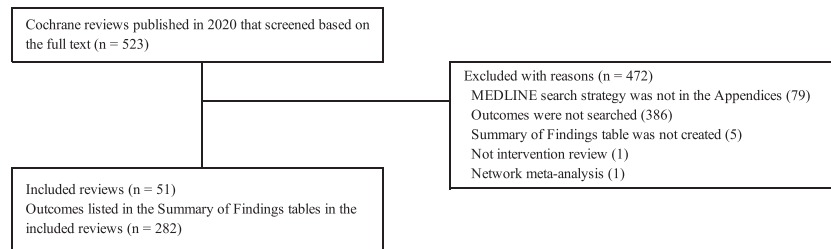


Fig. 1. Flow diagram of the present study.

2.5. Statistical analysis

We conducted a descriptive analysis on the main outcomes and tabulated the characteristics of the considered reviews that included outcomes in their search strategies as a necessary term. As for the considered reviews with the outcomes listed in the SoF tables, we compared the characteristics of outcomes that were implemented in search strategies with those that were not. We employed the Mann-Whitney test and Pearson's chi-squared test for continuous and categorical variables. We expressed the continuous variables as medians (IQR (interquartile range)), while the categorical variables were expressed as numbers and percentages. All the analyses were conducted using the STATA 14.2 software package (StataCorp LP, Texas).

2.6. Patient and public involvement

No patients or members of the public were involved in this study, as it was designed to investigate the methodological practices used in systematic reviews.

2.7. Difference in the protocol and the review

Since the network meta-analyses and the standard Cochrane reviews use different SoF tables, we excluded the reviews with the network meta-analyses. This modification only excluded one review. Since most of the included reviews evaluated the outcomes other than those considered in their search strategies, we discarded our plan to compare the characteristics between those that did and those that did not.

3. Results

Fig. 1 illustrated a flow diagram for this study. As presented, we identified 523 Cochrane reviews on the interventions that were published in 2020. Of those, 51 (9.8%) included terms related to the studies' outcomes in their search strategies and were therefore included for analysis. A total of 282 listed outcomes were found in the SoF tables and were thus used in the analysis aimed at exploring the different characteristics between outcomes that were listed in the search strategies and those that were not.

Table 2 summarizes the characteristics of the 51 included reviews that used terms related to outcomes in their

search strategies. As shown, two-thirds of the included reviews were related to prevention. A median of 12 studies were included in these reviews. More than half of these reviews excluded one or more studies due to the wrong outcomes. Fourteen (27%) added new outcomes that were not addressed in the protocol or previous version of the review. One review only used MeSH terms as the search terms related to the outcomes [15]. The supplementary File 1 shows a citation list of the included reviews according to their specific Cochrane review groups. Only one review acknowledged the limitations associated with searching for outcomes. The researchers specifically explained this as follows:

"However, our search strategy did not include the term 'mortality'. It is possible that studies looked at oral hygiene care and all-cause mortality without mentioning 'VAP' or 'pneumonia', and these may not have been identified by our searches [16]."

Fig. 2 shows the distribution of the number of outcomes that were included in the search strategies and those that were not. As shown, 47 (92%) of the reviews that included outcome terms in their search strategies also assessed outcomes that were not included in those strategies. The median (IQR) numbers of outcomes included and not included in search strategies were 3 (2 – 4) and 4 (2 – 7), respectively. As shown in Table 3, the included reviews found qualitatively different results for outcomes that were included in search strategies and those that were not. Therefore, outcomes included in the search strategies tended to include a larger number of studies and show their effects in favor of the intervention. They also tended to be statistically significant and provide a certainty of evidence more often than outcomes that were not included in the search.

4. Discussion

We found that approximately 10% of the recent Cochrane reviews included terms related to the studies' outcomes in their search strategies. However, the limitations of this practice were rarely acknowledged in their respective discussions or GRADE assessments. Further, most reviews that implemented the outcome terms in their search strategies also assessed outcomes that were not included

Table 2. Characteristics of Cochrane reviews that included outcomes in their search strategies

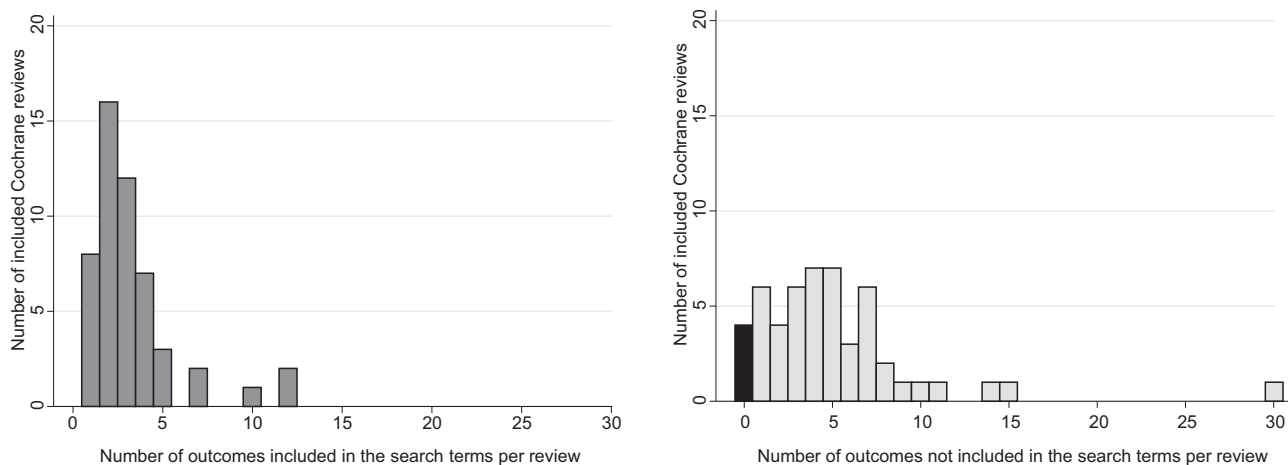
Characteristics	N = 51
Eligible study design	
RCTs only	25 (49)
RCTs and quasi-RCTs	12 (24)
RCTs, quasi-RCTs, and observational studies	14 (27)
Topic	
Prevention	34 (67)
Adverse event	1 (2)
Others [†]	16 (31)
Number of previous Cochrane reviews written by the first author	0 (0 – 29)
Involvement of an information specialist [*]	33 (65)
Number of records screened for titles and abstracts	1,932 (493 – 4,989)
Number of included studies	12 (6 – 32)
Studies excluded with the reason of wrong outcome	1 (0 – 8)
Adding outcomes that were not in the protocol or previous version of the review	14 (27)

Abbreviation: RCTs, randomized controlled trials; GRADE, the Grading of Recommendations Assessment, Development and Evaluation

Note: Values for continuous variables and categorical variables are given as number (percentage) and median (interquartile range).

^{*} The involvement of an information specialist was explicitly stated in the review.

[†] Topics other than prevention and adverse event

**Fig. 2.** Distribution of the number of outcomes included in the search strategy and those that were not

The median (interquartile range) number of outcomes included in the search strategy (left) and those that were not (right) numbered 3 (2 – 4) and 4 (2 – 7), respectively. A total of four Cochrane reviews did not assess outcomes other than those included in their search strategies (See the black bar in the right figure). An outcome in the search strategy was defined as a case, where the terms related to the outcome were included in the search strategy and were combined with the terms related to the participants or interventions via “AND.”

in those strategies. Outcomes that were included in the search strategies tended to differ from those that were not included.

It is widely accepted that the practice of including the terms related to outcomes in the search strategy creates problems due to the risk of overlooking the evidence [2,4,11]. However, we found approximately ten percent of the Cochrane reviews searched for outcomes without acknowledging the associated limitations. Based on the previous report showing that the inclusion of outcomes in the search strategies may result in lower retrieval of the rele-

vant evidence, we suggest that the authors who decide to search for outcomes should both justify this decision and comment on the potential limitations [4].

It should also be noted that we do not intend to criticize researchers merely for including terms related to outcomes in their search strategies. This is since we recognize that reviews with broad scopes of interest must often do this to remain feasible. For example, this includes cases such as: “Interventions for preventing venous thromboembolism in adults undergoing knee arthroscopy” and “Education and training for preventing and minimizing workplace aggres-

Table 3. Comparison of outcomes included and not included in search strategies listed in the SoF tables

	Outcomes in the search strategies* (n = 160)	Outcomes not in the search strategies† (n = 122)	P-value‡
Number of studies reported the outcome	2 (1 – 5)	1 (1 – 4)	0.026
Statistical significance			
Non significant	66 (41.2)	48 (39.3)	<0.001
Significant	57 (35.6)	21 (17.2)	
Can't tell§	37 (23.1)	53 (43.4)	
Direction of the effect			
Favored control	30 (18.8)	27 (22.3)	<0.001
Favored intervention	97 (60.6)	41 (33.9)	
Can't tell§	33 (20.6)	53 (43.8)	
GRADE certainty of evidence			
Very low	51 (31.9)	40 (32.8)	0.014
Low	46 (28.7)	23 (18.9)	
Moderate	25 (15.6)	14 (11.5)	
High	16 (10.0)	9 (7.4)	
Can't tell§	22 (13.8)	36 (29.5)	

Abbreviation: SoF, summary of findings; GRADE, the Grading of Recommendations Assessment, Development and Evaluation

Note: Values for continuous variables and categorical variables are given as number (percentage) and median (interquartile range).

* The terms related to review outcomes were in their search strategy and combined with terms related to participants or interventions by “AND”.

† The terms related to review outcomes were not in their search strategy.

‡ P-value for the Mann-Whitney test and Pearson's chi-squared test.

§ No description, no effect estimate, or only narrative summaries were provided.

||| Direction of the effect indicated by the point estimation irrespective of statistical significance

sion directed toward healthcare workers.” Neither of these could have narrowed the number of records through the search strategies that were solely focused on their respective participants and interventions [17,18]. As such, searching for outcomes might be the results of careful considering the type of question. Nevertheless, the practice of including outcomes may still overlook relevant studies, thus warranting acknowledgement and discussion.

We found that reviews which searched for outcomes usually also evaluated outcomes that were not included in their search strategies. In this context, the findings for outcomes that were included in these strategies significantly differed from those that were not included. More specifically, outcomes that were included in search strategies were more likely to have results that favored the intervention and were statistically significant, when compared with those that were not included. This may be due to a selective non-reporting bias, where positive results tend to be reported by publications, especially in abstract [8,9]. Indeed, relatively fewer studies reported outcomes that were not included in their search strategies. This may contribute to the reviews' findings being inconclusive. Alternatively, the relative importance and nature of these outcomes may vary. In Cochrane reviews, authors choose up to seven outcomes for the SoF tables but can only have up to three primary outcomes [2]. Therefore, it is unlikely that all outcomes examined in the present study were primary out-

comes in the included reviews. Focusing on the outcomes in the SoF tables, instead of the primary outcomes of the review, our study may have diluted the distinction between those searching the outcome terms and those not searching them, because typically the outcome terms included in the search represented the primary outcomes and not necessarily all the outcomes in the SoF tables. Although Cochrane's authors are encouraged to include the most critical and/or important health outcomes in their SoF tables, undesirable outcomes, such as adverse events or dropouts may not be included in their search strategies [2]. Additional research is needed to clarify how the inclusion of all outcomes of interest within the search strategy alter the reviews' findings and/or the conclusions of the systematic reviews.

We acknowledge that this study had several limitations. First, we only included the Cochrane reviews on the interventions with MEDLINE search strategies listed in their appendices. As several studies have reported that Cochrane reviews are of a better methodological quality than others [19,20], it was not considered plausible that the practice pattern of searching for outcome in non-Cochrane reviews would be more optimal than in Cochrane reviews. However, the reviews conducted by several Cochrane groups (e.g., the Pregnancy and Childbirth Group or Schizophrenia Group) only searched within their own specialized registers. They did not report MEDLINE search strategies in their appendices. The exclusion of these reviews

may have affected the disease area or nature of the outcomes. Second, although we determined if each outcome was searched or not by independent review of the MEDLINE search strategy including MeSH terms and free texts, there might be a misclassification. An outcome that was classified as “not searched” might be “searched” by exploding all the tree structures of medical subject headings or by searching other databases than MEDLINE. Third we did not take into consideration the potentially different nature of comparisons. For example, we extracted the intervention and control as they were presented in the first SoF table. However, whether an active or inactive comparator was used might affect the likelihood of resulting in a statistically significant effect. Fourth, although a previous study reported that searching for outcomes would miss 10%–20% of the available evidence [4], the researchers in question considered the Cochrane reviews regardless of whether they included outcomes in their search strategies. We were unable to confirm this assertion in our sample, as we did not attempt to search the literature *de novo* without outcomes in the search strategy. Future research should investigate whether the recall is similarly low for reviews, where the authors and information specialists decide to include outcomes in their search strategies.

Despite these limitations, there were also several strengths. To the best of our knowledge, this was the first study to show the current nature of searching for outcomes in the recent Cochrane reviews. Notably, we found that the limitations of searching for outcomes were often ignored by researchers, thus highlighting problems associated with assessing a mixture of outcomes that were and were not included in their search strategies. This study also employed a valid methodology with a pre-specified protocol, and followed the relevant reporting guidelines [12,13].

5. Conclusions

In this study, we examined the issues related to the current practice of including outcomes in the search strategies when conducting the Cochrane reviews. We found that many researchers did not mention any problems that arose as a result. The systematic reviewers who decided to include the terms related to outcomes in their search strategies should make a point of acknowledging the limitations. Further, many recent Cochrane reviews that have searched for outcomes evaluated those that were and were not included in their search strategies. Additional research is needed to determine if and to what extent conclusions are changed when all outcomes of interest are included in their search strategies.

Contributors

YTsuji had full access to all data used in the study and takes responsibility for both the integrity of the data

and the accuracy of the data analysis. YTsuji, YTsuji, YK, MB, and TAF developed the study's concept and design. YTsuji, YTsuji, YK, and MB acquired the data. YTsuji, YTsuji, YK, MB, and TAF analyzed and interpreted the data. YTsuji, YTsuji, YK, MB, and TAF drafted the manuscript. TAF critically revised the manuscript for important intellectual content. All the authors provided their final approval of the version submitted for publication and agreed that they were accountable for all aspects of this study.

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Ethical approval

Not required.

Data sharing

The dataset is available from the corresponding author upon request.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at [doi:10.1016/j.jclinepi.2021.08.030](https://doi.org/10.1016/j.jclinepi.2021.08.030).

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