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Research Article

THE OUTCOME EFFECT REPORTING BIAS IN RANDOMIZED CONTROLLED STUDIES ON A COHORT OF SYSTEMATIC REVIEWS

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Abstract:

To examine the prevalence of consequence stating bias, the selection for publication of a subset of the original recorded outcome variables on the basis of the results and its impact on Cochrane reviews. A nine-point classification system for missing outcome data in randomized trials was developed and applied to the trials assessed in a large, unselected cohort of Cochrane systematic reviews. A sensitivity analysis was undertaken to assess the impact of outcome reporting bias on reviews that included a single meta-analysis of the review of primary outcome. More than half (157/283 (55%)) the reviews did not include full data for the review primary outcome of interest from all eligible trials. The median amount of review outcome data missing for any reason was 10%, whereas 50% or more of the potential data were missing in 70 (25%) reviews. It was clear from the publications for 155 (6%) of the 2486 assessable trials that the researchers had measured and analyzed the review primary outcome but did not report or only partially reported the results. For reports that did not mention the review primary outcome, our classification regarding the presence of outcome reporting bias was shown to have a sensitivity of 88% (95% CI 65% to 100%) and specificity of 80% (95% CI 69% to 90%) on the basis of responses from 62 trialists. A third of Cochrane reviews (96/283 (34%)) contained at least one trial with high suspicion of outcome reporting bias for the review primary outcome. In a sensitivity analysis undertaken for 81 reviews with a single meta-analysis of the primary outcome of interest, the treatment effect estimate was reduced by 20% or more in 19 (23%). Of the 42 meta-analyses with a statistically significant result only, eight (19%) became non-significant after adjustment for outcome reporting bias and 11 (26%) would have overestimated the treatment effect by 20% or more. Outcome reporting bias is an under-recognized problem that affects the conclusions in a substantial proportion of Cochrane reviews. Individuals conducting systematic reviews need to address explicitly the issue of missing outcome data for their review to be considered a reliable source of evidence. Extra care is required during data extraction, reviewers should identify when a trial reports that an outcome was measured but no results were reported, or events observed and contact with trialists should be encouraged.

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INTRODUCTION:

Discerning reporting bias in a research is described as the choice, based on the effects, of a subset of analyses for being revealed. Discerning reporting could happen in reference to outcome analyses, subgroup analyses, and per method analyses, in the place of purpose to deal with analyses, in addition to various other analyses. Three categories of discerning reporting of results occur: the selective reporting of several group of study outcomes, if not all examined outcomes are reported; the selective reporting of the particular outcome for instance, when an outcome is assessed and examined at several time points though not all outcomes are reported; and imperfect reporting of a selected outcome for instance, when the main difference in means around treatments is reported to get an outcome but no traditional error is provided with.

A particular form of bias as a result of the selective reporting of the group of study outcomes is outcome reporting bias, that will be defined as the choice for release of a part of the authentic recorded outcome factors based on the results. Experimental study on randomised controlled trials demonstrates intense proof of a connection between important results and publication: scientific studies that report favorable or significant results ($P < 0.05$) are more inclined to be published, and results that are statistically important have higher chances of being fully reported as opposed to those that are not significant (range of odds ratios: 2.2 to 4.7).

An evaluation of researches that reviewed experiment publications with protocols discovered that 40-62% of trials modified, introduced, or overlooked a minimum of primary outcome. The organized review process was created to reduce biases and random glitches through the review of health care interventions. Cochrane systematic reviews are globally acknowledged as among the ideal means, if

not the best source, of dependable updated facts on health care. Meta-analysis, a analytical way of incorporating is a result of multiple associated but separate studies, can generate significant efforts to medical research such as, by revealing that there surely is explanation to give hope to treatments not regularly used or that evidence is missing to support treatments which are in wide use. Missing result data impacts a methodical review in two ways. Publication bias, where research is not released based on its results, can cause bias in the analysis of the specific outcome in a review, particularly if the conclusion to never publish or submit the research relates to the results for that outcome.

In a published study that has been identified by the reviewer, outcome reporting bias can arise if the outcome of interest in the review had been measured and analysed but not reported on the basis of the results. Little is known about the impact of outcome reporting bias on systematic reviews. One previous study examined a small cohort of nine Cochrane reviews of randomized trials. Although outcome reporting bias in the review primary outcome was suspected in several individual randomized trials, the impact of such bias on the conclusions drawn in the meta-analyses was minimal. This study used a very select set of reviews, however, and highlighted the need for a larger study. In this paper we report the findings of the Outcome Reporting Bias in Trials (ORBIT) study, in which we applied a new classification system for the assessment of selective outcome reporting and evaluated the validity of the tool. We used the classification system to estimate the prevalence of outcome reporting bias and its impact on an unselected cohort of Cochrane reviews. To our knowledge, this is the first systematic empirical study of the impact of outcome reporting bias in randomized controlled trials on the results of systematic reviews.

Table 1 | Example of a review outcome matrix displaying the information available in trial reports

Trial ID (author, year of publication)	Review primary outcome	Other review outcomes		Additional outcomes (reported in any of the eligible trials)		
		Chemical pregnancy rate	Clinical pregnancy rate	Ectopic pregnancy rate	Birth weight of baby	Reason for exclusion
12345678.1 (Smith, 1999)	o	x	√	x	x	—
12345678.2 (Lowe, 2001)	√	o	x	√	x	—
12345678.3 (Biggs, 2004)	x	√	√	x	√	—
...						
Excluded trials						
1234578.9 (Johns, 2006)	x	x	x	x	x	No relevant outcome data
...						

√ Full reporting of results for treatment comparison of interest.

x No reporting of results for treatment comparison of interest.

o Partial reporting of results for treatment comparison of interest.

METHODS:

We analyzed an unselected cohort of the latest feedback from 50 of the 51 Cochrane combination review groups released in three issues of the Cochrane Library (Issue 4, 2016, Issue 1, 2017, and Issue 2, 2017). For every review, a couple of investigators (JJK and SD) separately analyzed the sorts of outcome strategies segment to find out perhaps the review designated a single primary result. For people reviews where perhaps no primary outcome was comprehensive or numerous primary results were designated, the lead reviewer was approached and expected to choose a single primary outcome from those indexed. When no contact could be established or the reviewer(s) could not define a single primary outcome, two investigators (PRW and SD) independently selected and agreed upon a single primary outcome from those listed.

Assessment of systematic reviews:

A couple of investigators (JJK and SD) inspect all 33 reviews from Issue 4, 2016 which designated a specific primary impact and decided on the requirement of additional evaluation of most of but two reviews. Both arguments were pertaining to perhaps the reasons for exemption were effective of outcome revealing bias. Each leftover review was read by one researcher (JJK) to confirm whether all incorporated tests fully revealed the review main result. The reason for exemption about any trial (in the attributes of omitted studies section) has also been verified for any suggestion of possible result reporting bias. As an example, an effort excluded since there was no appropriate outcome data involved more analysis since the relevant outcome may have been assessed but not reported. Any concerns about the omitted research were considered PRW. Reviews

that did not recognize any randomized managed studies have not been evaluated further. Likewise, reviews have not been assessed additionally if no standard concise explanation of the main consequence prevails, because outcome reporting bias assessment in this situation would be impossible. One example is relapse in schizophrenia trials, for which definitions include a change in symptom score and hospital readmission.

Classification of randomized controlled trials in systematic reviews:

For every review, an end result matrix was created revealing the reporting on the primary outcome besides other outcomes in each sample incorporated, identifying full, partial, or no reporting. An illustration of an outcome matrix is provided with in table 1. For such an example, “live birth” was the review main outcome. The array was accomplished making use of the facts through the review and modified accordingly in light associated with an additional information obtained based on the trial reports or through contact with the trialists. Outcomes for which the data could be included in a meta-analysis were considered to be fully reported. Such data may have been in the trial report or may have been calculated indirectly from the results. For example, the number of events may have been calculated from the proportion of events and the number of patients in the treatment group, or the standard error of the treatment effect may have been calculated from the estimate of effect and the associated P value.

A classification system was designed to evaluate the potential risk of bias when a trial was excluded from a meta-analysis, either because the data for the

outcome were not reported or because the data were reported incompletely (for example, just as “not significant”). The system was refined over the initial few months of the study, but if an amendment was made all previous classifications were reviewed and

adjusted as appropriate to ensure consistency of application. The categories reflect the stages of assessing whether an outcome was measured, whether an outcome was analysed, and, finally, the nature of the results presented (table 2).

Table 2 | The Outcome Reporting Bias In Trials (ORBIT) study classification system for missing or incomplete outcome reporting in reports of randomised trials

	Description	Level of reporting	Risk of bias*
Clear that the outcome was measured and analysed			
A	Trial report states that outcome was analysed but only reports that result was not significant (typically stating $P>0.05$)	Partial	High risk
B	Trial report states that outcome was analysed but only reports that result was significant (typically stating $P<0.05$)	Partial	No risk
C	Trial report states that outcome was analysed but insufficient data were presented for the trial to be included in meta-analysis or to be considered to be fully tabulated	Partial	Low risk
D	Trial report states that outcome was analysed but no results reported	None	High risk
Clear that the outcome was measured			
E	Clear that outcome was measured but not necessarily analysed. Judgment says likely to have been analysed but not reported because of non-significant results	None	High risk
F	Clear that outcome was measured but not necessarily analysed. Judgment says unlikely to have been analysed but not reported because of non-significant results	None	Low risk
Unclear whether the outcome was measured			
G	Not mentioned but clinical judgment says likely to have been measured and analysed but not reported on the basis of non-significant results	None	High risk
H	Not mentioned but clinical judgment says unlikely to have been measured at all	None	Low risk
Clear that the outcome was not measured			
I	Clear that outcome was not measured	NA	No risk

*Risk of bias arising from the lack of inclusion of non-significant results when a trial was excluded from a meta-analysis or not fully reported in a review because the data were unavailable.

The system identifies whether there is evidence that the outcome was measured and analysed but only partially reported (A to D classifications), whether the outcome was measured but not necessarily analysed (E and F), if it is unclear whether the outcome was measured (G and H), or if it is clear the outcome was not measured (I). A “low risk” classification was awarded when it was suspected, but not actually known, that the outcome was either not measured, measured but not analysed, or measured and analysed but either partially reported or not reported for a reason unrelated to the results obtained. A “no risk” classification was reserved for cases where it was known that the outcome was not measured, known that it was measured but not analysed, or known that it was measured and analysed but the reason for partial or no reporting was not because the results were statistically non-significant. For cases where the outcome was measured but not necessarily analysed, judgment was needed as to whether it was likely (E) or unlikely (F) that the measured outcome was analysed and not reported because of non-significant results. When it was unclear whether the outcome was measured,

judgment was needed as to whether it was likely that the outcome was measured and analysed but not reported on the basis of non-significant results (G) or unlikely that the outcome was measured at all (H). Trials classified as A/D/E/G, C/F/H, and B/I were assumed to be at high, low, and no risk of outcome reporting bias, respectively, in relation to the review primary outcome. Examples of each of the classifications in the ORBIT study are shown in web table A.

Accuracy and Classification:

For studies that it was confused whether the analysis primary result had even been assessed and/or analysed (E, F, G, or H classification; table 2), the trialists had been approached through e-mail (address taken from either the test report or even a search of PubMed or Google) and also asked to verify perhaps the review primary result was assessed and analysed. If so, the reason behind not reporting the effects was requested. Non-responders were approached another time if the response had not been obtained within three weeks. Trialists were not approached if a

reviewer had previously approached them for the relevant information.

Two individual sensitivity and specificity comparisons had been performed. The primary analysis considered exclusively G and H categories and directed to regulate how good our distinction system was at judging whether the primary outcome of interest in the review had been measured when it was not mentioned in the trial report. For this analysis only, we incorporated an extra category of G classification for trials with binary outcomes where we predicted that the outcome was measured but it was not reported because there were no events. The second analysis compared our classifications with information from the trialists to establish whether we could predict if biased reporting had occurred. Implicitly, E and G classifications suggested that bias was likely because it was either clear or assumed that the outcome had been measured and possible that non-reporting could have been influenced by the non-significance of the result. These classifications were taken to imply bias on the basis of the lack of inclusion of non-significant results. The specificity was calculated taking F and H classifications to indicate no bias. This analysis excluded any studies classified as F that were ongoing because it is difficult to assess bias until a study is completed. Confidence intervals for sensitivity and specificity estimates were calculated using standard formulas.

Amount and Impact of Missing Trial Data:

The amount of missing data per review was calculated, firstly on the basis of trials that omitted data for any reason and secondly only using those trials where data omission was suspected on the basis of the results (that is, outcome reporting bias was suspected). The maximum bias bound approach was used in a sensitivity analysis to estimate the impact of outcome reporting bias on the review meta-analysis. This approach calculates an upper bound for the bias resulting from the number of eligible studies suspected of outcome reporting bias, and assumes that on average smaller studies (lower precision) will have a higher probability of not reporting the outcome of interest than larger studies (higher precision). This method was applied only to reviews that had a single meta-analysis of the review primary outcome, because if there were multiple meta-analyses it would be difficult to ascertain to which analyses the trial with suspected outcome reporting bias would relate without discussion with a clinical expert. The impact was not assessed for trials with H or I classifications, where it was suggested that the review primary outcome had not been measured, or G classifications where the explanation was that there were no events. The impact was assessed both in terms of the percentage change in the treatment effect estimate and the change in the statistical significance of the treatment effect estimate after adjustment.

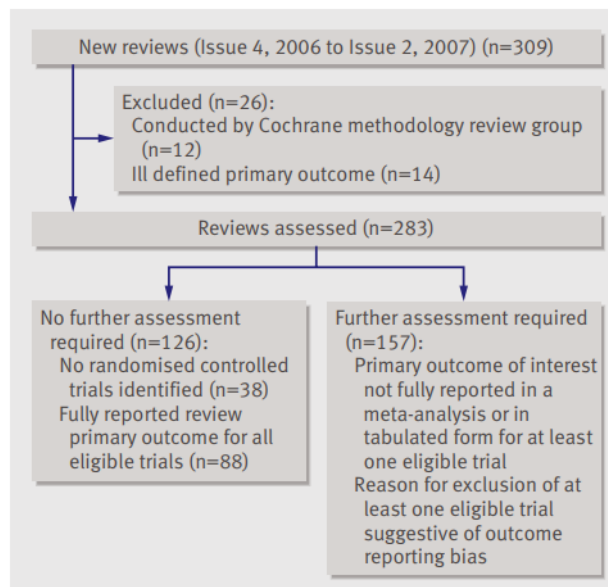


Fig 1 | Flow diagram for Outcome Reporting Bias In Trials (ORBIT) study

RESULTS:

Assessments of systematic reviews:

The Cochrane Library exhibited 309 latest reviews in Issue 4, 2016, Issue 1, 2017, and Issue 2, 2017 (fig 1). We omitted 12 feedback by the Cochrane

Methodology Review Group. Single major outcomes had been designated in 103 feedback, while lead evaluators or co-reviewers had been expected to choose a single biggest result for the residual 194 reviews. In 173 cases reviewers were willing to do so, with 127 (73%) choosing the first outcome listed. For the remaining 21 reviews a single primary outcome was selected by the research team (PRW and SD). On further examination, nevertheless, 14 feedback were omitted considering that the review main result was not well defined. Among the residual 283 feedback, the average number of feedback from an individual Cochrane overview group was five (range 1 to 21, interquartile range (IQR) 2 to 7). The five groups with many feedbacks had been the hepato-biliary group (21 reviews), the pregnancy and childbirth group, the neonatal group, the oral health group, and the menstrual issues and subfertility group. The average volume of randomised controlled studies per review was five (range 0 to 134, IQR 2 to 10). A total of 126 reviews did not require further assessment: 38 did not identify any randomised controlled trials and 88 fully reported the primary outcome for all eligible trials. This left 157 reviews

requiring further assessment—that is, 55% (157/283) of reviews did not include full data on the primary outcome of interest from all eligible trials.

Full reporting of review primary outcomes in trials:

Figure 2 demonstrates a flow diagram for the evaluation of the 2562 trials involved in the examine cohort of 283 organized reviews. Seventy-six trial reports could hardly be evaluated as the content have not been in English. Seventy-one per cent (1774/2486) of the other studies completely reported the review primary result in the trial report. Table 3 supplies information on 177 trial reports that offered complete data on the main outcome of interest that was not included in the review. For 59 trials, the data were not included in the review for a reason unrelated to outcome reporting bias. For 118 trials (7% of the 1774 trials that fully reported the review primary outcome), the review primary outcome data were fully reported in the publication but were not included in the review. Information on missed outcome data was fed back to the reviewers for inclusion in a review update.

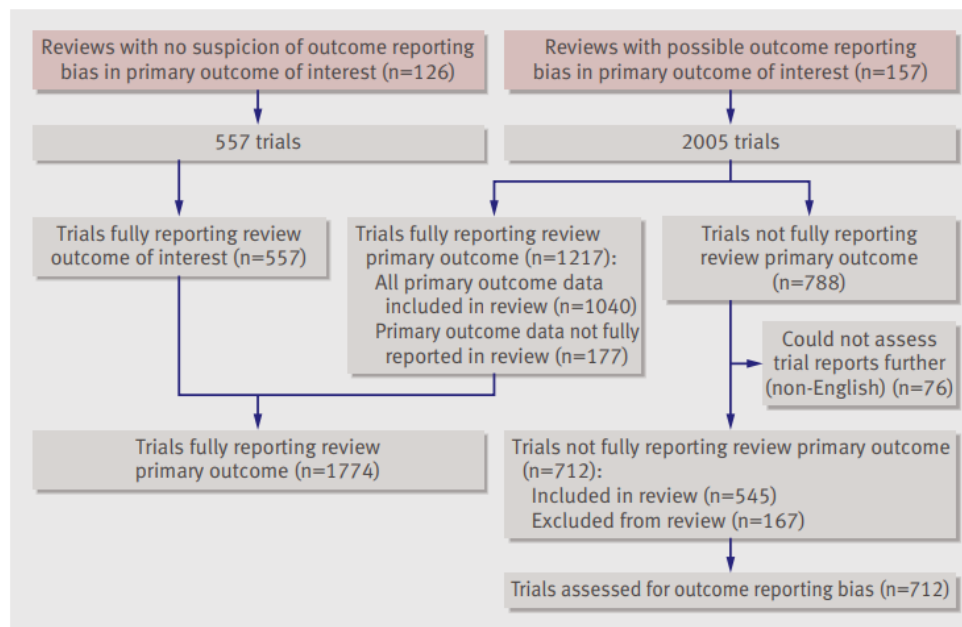


Fig 2 | Assessment of randomised controlled trials within reviews

Classification of trials:

For 788 (31%) of the 2562 trials included in our study, the review primary outcome was either partially reported or not reported (fig 2). Seventy-six trial reports could not be assessed because the articles were not in English, leaving 2486 assessable trials and 712 trial reports requiring a classification (545

included in reviews and 167 excluded from reviews). Table 4 shows the classification of these 712 trials. For 155 (6%) of the 2486 assessable trials, it was clear that the review primary outcome was measured and analysed (A, B, C, or D classification), but partial reporting meant the data could not be included in a meta-analysis. Trials classified as C were grouped

according to the nature of the missing data (web table B). A total of 359 (50%) of the 712 trials with missing data were under high suspicion for outcome reporting bias (A, D, E, or G classification; table 4). The prevalence of reviews containing at least one trial with high outcome reporting bias suspicion was 34% (96/283).

Accuracy of classification:

Information on whether the outcome of interest was measured and analysed was lacking in 538 trial reports (E, F, G, or H classification). Researcher found the email addresses of 167 (31%) authors and contacted these individuals. Responses were received from 65 authors (39%): 26% (9/34) of authors whose trial had an E classification; 33% (1/3) who got an F classification; 42% (30/71) who got a G classification; and 42% (25/59) of individuals from trials with an H classification. To determine whether the outcome of interest was measured or not, researcher compared the assessments against the

trialists' information for 55 trials for which the outcome had not been mentioned in the trial report (G or H classification). The sensitivity for predicting that the outcome had been measured was 92% (23/25, 95% CI 81% to 100%), whereas the specificity for predicting that the outcome had not been measured was 77% (23/30, 95% CI 62% to 92%; table 5).

To measure this study's judgment on whether outcome reporting bias occurred or not, researcher compared the assessments against the trialists' information for 62 trials for which the outcome was either clearly measured but not necessarily analysed (E and F classification) or had not been mentioned in the trial report (G or H classification). Three ongoing studies were excluded from this analysis. The sensitivity of the classification system for detecting bias was calculated to be 88% (7/8, 95% CI 65% to 100%), whereas the specificity was 80% (43/54, 95% CI 69% to 90%; table 7).

Table 3 | Reasons for omission of data from trials fully reporting review primary outcome (n=177)

Reason	Number of trials
Data not included in review for a reason unrelated to outcome reporting bias (n=59)	
Invalid measurement scales	4
Poor reporting of time to event data	31
Quality issues	24
Data not included in review despite being fully reported in trial (n=118)	
Not fully reported in the review text*	29
No event*	31
No results reported in review*	58

Table 4 | Trials assessed for outcome reporting bias (n=712)

Classification	Number of fully published trials	Number of abstracts	Total number of trials (%)
A	23	7	30 (4)
B	2	6	8 (1)
C	113	4	117 (16)
D	0	0	0 (0)
E	113	9	122 (17)
F	24	9	33 (5)
G	192	15	207 (29)
H	148	28	176 (25)
I	15	4	19 (3)
Total	630	82	712

Table 5 | Accuracy of judgment as to whether the review primary outcome was measured (G or H classification)

			Information from trialist		Total
			Primary outcome measured	Primary outcome not measured	
ORBIT assessment	Primary outcome measured	G classification	4	7*	11
		G classification (no event)	19	0	19
		Total	23	7	30
	Primary outcome not measured	H classification	2*	23	25
Total			25	30	55

DISCUSSION:

Outcome reporting bias was suspected in at least one randomised controlled trial in more than a third of the systematic reviews we examined (35%), which is substantially higher than the number of reviews in which a reference to the potential for outcome reporting bias was found (7%), thus demonstrating under-recognition of the problem. Researcher has also shown through sensitivity analysis that outcome reporting bias affects the treatment effect estimate in a substantial proportion of Cochrane reviews.

Strengths and limitations of the study:

The strengths of the study are that researcher evaluated a large, unselected cohort of reviews, review authors were involved in the assessment of outcome reporting bias, and the author of the trial included in the reviews was contacted for information. In addition, the textual justification for each trial classification was checked by a senior investigator. Researcher undertook an internal pilot study of 33 reviews to determine the level of agreement between two researchers on the need for further assessment of a review for suspicion of outcome reporting bias. Given that agreement was high, researcher concluded that it would be sufficient for a single reviewer to assess the remainder of the reviews, provided a second reviewer checked the reasons for excluded studies where there was uncertainty. For the majority of trials that were missing outcome data, judgment was needed regarding the potential for outcome reporting bias.

CONCLUSION:

This particular summary, though, depends on the presumption which trialists researcher approached provided precise facts to us. A past research advised that trialists might be hesitant to admit discerning reporting. Within this research, the response rate for

all trialists for whom an e-mail address was received was matching in trials which includes a dangerous category and those with a low risk category. If response bias was functioning, researcher supposed the susceptibility of categories to be disregarded (because of trialists with high risk classifications being less probably to reply when they have precisely revealed results) and also uniqueness overestimated (due to the trialists with low risk categories being apt to respond when they have not selectively reported results). With such response bias, the volume of selectively reported trials using a review will be underestimated; thus understanding outcome stating bias on the findings of the reviews studied here might have been underestimated. The classifications of trials for outcome reporting bias facilitated an assessment of the robustness of review conclusions to such bias. The maximum bias bound approach was the method chosen to examine this source of bias because it can be applied to any outcome type. Although only 81 (29%) of the 283 reviews studied comprised a single meta-analysis of the primary outcome of interest and were thus included in the assessment, there is no reason to believe the results of this assessment would not be generalizable to those reviews containing multiple meta-analyses of the primary outcome relating to different treatment comparisons. However, there is a limitation of study such as it has not examined how the impact of outcome reporting bias should be assessed in reviews that do not include a meta-analysis.

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