

Inconsistencies are common between non-Cochrane systematic reviews and their protocols registered in the International prospective register of systematic reviews (PROSPERO) but were seldom explained

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Abstract

Background: Protocols of systematic reviews allow for planning and documentation of review methods and thus improve the transparency of the reviews process. However, pre-registration of a protocol is not enough, the author also need to follow it. PROSPERO is an open-access online database for the registration of non-Cochrane systematic reviews. The purpose of this study is to compare published non-Cochrane reviews with their pre-registered protocols on PROSPERO to determine what changes, if any, have been made, and how likely these changes are to impact the quality of systematic review. **Methods:** This is a retrospective comparative study. We searched for protocols on PROSPERO platform that were registered in 2018 and then selected the protocols that full text have been published as of January 1st 2019. Published full texts were identified through the protocol's final publication citation. Two authors independently compared and identified changes between protocols and systematic reviews and then evaluated the impact (improve, reduce, or unclear) of these changes on the reporting or methodology quality of reviews. Descriptive statistics of percentage (%) and frequency (n) were conducted. **Results:** We identified 39 pairs, all of which exhibited changes. "Search strategy"(92%, n=36), "data extraction"(90%, n=35), "data synthesis"(77%, n=30), "outcome"(64%, n=24), and "subgroup analysis"(64%, n=24) all showed significant changes. All changes to only one review were considered to improve the reporting or methodology quality, and the remaining 97% of reviews (n=38) contained changes that were considered to reduce the methodology or reporting quality or that had an unclear impact on systematic reviews. **Conclusions:** Changes between the non-Cochrane systematic reviews and their protocols recorded on PROSPERO were widespread. Some of the changes reduced the methodology or reporting quality of systematic reviews or had an unclear impact. Measures should be taken to further improve the transparency of the non-Cochrane systematic reviews. Adding a new item in updated "Preferred Reporting Items for Systematic reviews and Meta-Analyses" (PRISMA) and "Meta-analysis of Observational Studies in Epidemiology" (MOOSE) to guide reporting and explaining the changes, as well as advising peer reviewers (and editors) to check the reviews against the protocols are two suggested fundamental solutions.

Background

Systematic review is the cornerstone of evidence-based health care and is widely promoted as providing the best evidence for informed decision-making[1-3]. However, due to the nature of retrospective studies, the problem of selective reporting outcomes and selective inclusion must be addressed at the level of systematic reviews[4-6]. Protocols of systematic reviews allow for planning and documentation of review methods, serve as guards against arbitrary decision making during review conduct, and enable readers to assess the presence of selective reporting against completed reviews[5-8].

Prior to 2011, only a few organizations, including the Cochrane Collaboration Organization and the Joanna Briggs Institute (JBI), provided a registration platform for systematic reviews to reduce the occurrence of bias and ensure the transparency of the systematic review production process. Some researchers evaluated the methodological quality of non-Cochrane and Cochrane systematic reviews and

found that Cochrane reviews as a whole are of higher methodological quality than non-Cochrane reviews published in peer-reviewed journals[9,10]. However these organizations only publish a minority of systematic reviews[3], and there are still no mandatory registration policies for most systematic reviews. To effectively fill the vacancy of systematic review registration platforms and improve the transparency of non-Cochrane systematic reviews, the international prospective register of systematic reviews (PROSPERO) was developed and launched by the United Kingdom Centre for Reviews and Dissemination in 2011[11,12]. PROSPERO is an open-access online database for the registration of non-Cochrane systematic reviews. Registration on PROSPERO involves submission and publication of key information about the design and conduct of a review, which includes information on 22 mandatory and 18 optional items[11,13] that were selected according to international consultation[14].

Recent data suggests that more than 8,000 systematic reviews are indexed in MEDLINE annually, representing a three-fold increase over the last decade[3]. Meanwhile, the differences between the published full-text and the pre-registered protocols have become a noteworthy issue. In 2002, an examination of Cochrane reviews revealed indirect evidence for possible selective reporting bias in systematic reviews[15]. The study compared 47 completed Cochrane reviews with their published protocols and demonstrated that 91.5% of the reviews (n=43) contained major changes in methodology. Up to December 31st, 2018, there were a total of 45,638 systematic reviews registered on PROSPERO, among which 3,976 were published[16]. To our knowledge, no study to date has compared the texts of published systematic reviews with their protocols registered on PROSPERO. Additionally, unlike the Cochrane library's rigorous assessment of registered protocols, PROSPERO has no quality assessment or peer review process for submitted protocols[17]. As such, the purpose of our study is to compare published non-Cochrane reviews with their pre-registered protocols on PROSPERO to determine what changes, if any, have been made to methodology-related sections and how likely these changes may impact the quality of systematic review.

Methods

Eligibility criteria

We included systematic reviews that met the following criteria: (1) pre-registered on PROSPERO between January 1st and December 31st of 2018; (2) included intervention studies (randomized or non-randomized controlled trials) or observational studies (e.g., cohort studies, case-control studies, and cross-sectional studies); (3) were published in English. We excluded Cochrane systematic reviews, JBI systematic reviews, and systematic reviews which included non-clinical studies.

Identification and selection of protocols and reviews

The search strategy was developed and executed by one author (K-YH) on January 1st 2019. The following filters of PROSPERO platform were used to initially identify eligible protocols: (1) Source of the review, all protocols excluded Cochrane protocols; (2) Status of review, published; (3) Data added to

PROSPERO, 01/01/2018-31/12/2018. These records most often included a citation and link to the final publication. For invalid link, we manually searched for the reviews in open databases (PubMed, Embase, and Web of Science) using the title of final publication. After identification of a published review, we obtained the latest version of protocol. Then, two authors (K-YH and W-YZ) examined the full-text of all “pairs” according to the eligibility criteria. If the author found two protocols registered for one published review, the corresponding author was contacted to confirm which protocol should be considered. Any remaining doubts were resolved through discussion with the third author (BM).

Difference assessment

For all included pairs, two authors (K-YH and TZ) independently examined relevant text, including related supplementary files, to compare methodology-related sections and to assess whether a difference existed. The difference assessment was based on an internal guideline that was developed, independently pilot-tested (in n=10 pairs), and revised by two authors (K-YH and BM) (Additional file 1). Before the formal assessment, a random sample of ten pairs was assessed by the two authors (K-YH and TZ), and the assessment did not commence until high agreement (>90%) was achieved. In case where differences were observed, two authors (K-YH and TZ) independently examined if the differences had been reported and explained in published reviews or the latest protocols. Any remaining disagreement was resolved through discussion with the third author (BM).

The following 13 methodology-related sections were compared and assessed: title, review question, search strategy, participants/population, intervention(s)/exposure(s), comparator(s)/control, types of study design, primary and additional outcome(s), study selection, data extraction, risk of bias (quality) assessment, strategy for data synthesis, and analysis of subgroups/subsets. These 13 sections are the mandatory registration entries required by PROSPERO.

Data extraction

Data extraction forms were developed in Microsoft Office Word 2016 software. The data were extracted independently and cross-checked by two authors (K-YH and TZ). For each pair, the text details where a difference existed were extracted from both protocol and publication. If the explanation for the difference was available, it was also extracted. Any discrepancies were discussed and resolved with the third author (BM).

Identification of change's impact and categories

The extracted text describing the difference was initially defined by one author (K-YH) to one of following types of change: adding, deleting, or modifying. Then, two authors (K-YH and QZ) independently evaluated the impact of these types of change on quality of systematic reviews. The impact on quality of systematic reviews included: (1) improving reporting or methodology quality; (2) reducing reporting or methodology quality; (3) unclear (the impact of changes on quality of systematic reviews can't be determined). Table 1 contains detailed information on this evaluation. Any changes where an

explanation was given, were considered to improve the reporting quality. We did not evaluate the contents of any changes (literature management software, statistical software, method to grade the quality of evidence, etc.) which was not mentioned in the current version of PRISMA[5] or MOOSE[18] or “A critical appraisal tool for systematic reviews that include randomized or non-randomized studies of healthcare interventions, or both” (AMSTAR2)[19]. The two authors (K-YH and QZ) cross-checked the evaluation results and discussed the discrepancies with the third author (BM). Based on the comparison and evaluation results, two authors (K-YH and QZ) summarized the final change categories for each methodology related section by discussion with the third author (BM).

Table 1. An internal guideline used to evaluate the impact of changes

le types of	Possible impact on quality of systematic review(s)	Explanation/example
g the minimal items of [A/MOOSE] additional information	Improve reporting quality	<ol style="list-style-type: none"> 1. Improving the transparency, e.g., adding the information sources in the search (such as databases with dates of coverage, contact with study authors to identify additional studies) and date last searched 2. Improving indexing and identification, e.g., inclusion of the terms “systematic review” or/and “meta-analysis” in the title
g the required process of AR2	Improve methodology quality	<ol style="list-style-type: none"> 1. Reducing the risk of bias, e.g., adding the manual search of grey literature; adding consensus process when disagreements arose in study selection 2. Improving the determination of the applicability of the results, e.g., adding the detailed eligibility criteria of PICO
g the minimal items of [A/MOOSE] additional information	Reduce reporting quality	<ol style="list-style-type: none"> 1. Reducing the transparency, e.g., deleting the information sources in the search (such as databases with dates of coverage, contact with study authors to identify additional studies) and date last searched 2. Reducing indexing and identification, e.g., exclusion of the terms “systematic review” or/and “meta-analysis” in the title
g the required process of AR2	Reduce methodology quality	<ol style="list-style-type: none"> 1. Increasing the risk of bias, e.g., deleting the manual search of grey literature; deleting consensus process when disagreements arose in study selection 2. Impacting the determination of the applicability of the results, e.g., deleting the detailed eligibility criteria of PICO
g the methods	Improve methodology quality	<ol style="list-style-type: none"> 1. Reducing the risk of bias: e.g., increasing databases, expanding time range of search, adding assessors performing data extraction
	Reduce methodology quality	<ol style="list-style-type: none"> 1. Increasing the risk of bias: e.g., reducing databases, narrowing time range of search, reducing assessors performing data extraction
	Unclear	<ol style="list-style-type: none"> 1. The impact on quality of systematic reviews can't be determined, e.g., modifying participants, interventions, comparators, outcomes, types of study design included, subgroup analysis; adding/deleting individual outcomes; deleting the distinction between primary and secondary outcome

PRISMA: Preferred Reporting Items for Systematic reviews and Meta-Analyses; MOOSE: Meta-analysis of Observational Studies in Epidemiology; AMSTAR2: A critical appraisal tool for systematic reviews that include randomized or non-randomized studies of healthcare interventions, or both; PICO: participant(s), intervention(s), comparator(s), outcome(s)

Data analysis

We performed a descriptive analysis using Microsoft Office Excel 2016 software. Results were reported as percentage (%) and frequency (n).

Results

Search results

15,667 non-Cochrane protocol records were registered on PROSPERO from January 1st to December 31st of 2018, and 43 reviews were completed and published on 1st January 2019. Of the 43 potentially relevant reviews, three reviews were excluded, two of which included non-clinical studies and one that was post-registered. We found one review that registered two different protocols (with the registration numbers CRD42018086539 and CRD42018084876), and determined the relevant one by contacting the author (Additional file 2). All excluded reviews are listed in Additional file 3. 39 systematic reviews[20-58] fulfilled the eligibility criteria and were subsequently included.

Categories and impact of changes in each section

All changes in the systematic reviews compared to their protocols were compiled (see Additional file 4). These changes involved all compared methodology-related sections, and the change categories as well as references reporting them were shown in Table 2. The “search strategy” section exhibited the greatest variation, with changes in 92% of the reviews (n=36). The “data extraction” and “data synthesis” sections also exhibited significant changes, with 90% of reviews (n=35) exhibiting changes in data extraction and 77% of reviews (n=30) exhibiting changes in data synthesis. Changes in the above sections primarily improved the methodology or reporting quality of systematic reviews. Moreover, 64% of reviews (n=25) exhibited changes in the “outcome” section and another 64% of reviews (n=25) exhibited changes in the “subgroup analysis” section. The changes in the above sections most often had an unclear impact on systematic reviews. Characteristic of impact for all changed reviews in each compared section is shown in Fig.1. Only 8% of included reviews (n=3) [22,43,54] provided the explanations for individual changes in the published full text and thus were considered to improve the reporting quality.

Table 2. Categories and impact of changes (n=39)

Categories of change	Improve the reporting/methodology quality	the	Reduce the reporting/methodology quality	the	Unclear
Inclusion of the terms "systematic reviews" and "Meta-analysis" in review title	[33] [43] [49]				
Exclusion of the terms "systematic reviews" and "Meta-analysis" from review title			[40] [46]		
The key information (PICO) about the scope of the reviews was provided	[21] [25] [31] [34] [38] [47] [49] [50] [53]				
The key information (PICO) about the scope of the reviews was deleted			[45] [48] [55]		
The key information (PICO) about the scope of the reviews was modified					[46] [56]
1 (4/39)					
Modifying the review question (modifying the intervention(s))					[25]
Narrowing the review question (deleting the intervention(s)/exposure(s))					[33] [46]
Expanding the review question (considering safety in addition to efficacy)					[49]
ria					
pulation (12/39)					
Modifying the participants					[45]
Deleting the eligibility criteria of included participants			[31] [34] [49] [56]		
Adding the eligibility criteria of included participants	[21] [24] [27] [32] [48] [53] [57]				
'exposure(s) (13/39)					
Modifying the intervention(s)/exposure(s)					[25] [33] [39] [46]
Adding the eligibility criteria of intervention(s)/exposure(s)	[21] [22]* [27] [30] [41] [44] [45] [48] [55]				

control (5/39)	
Modifying the control group	[33]
Deleting the eligibility criteria of control group	[27]
Adding the eligibility criteria of control group	[44] [57] [35]
/39)	
Modifying the outcome(s)	[28] [32] [33] [56]
Deleting the distinction between primary and secondary outcome(s)	[20] [21] [41] [42] [45] [49]
Adding/deleting individual primary or/and secondary outcome(s)	[20] [21] [22] [23] [27] [28] [30] [31] [33] [37] [41] [42] [43] [44] [45] [54]
Adding the measures/definition of outcome(s)	[25] [29] [37] [43] [53] [54] [55]
Deleting the measures/definition of outcome(s)	[22] [27] [34] [37] [38] [41] [49]
design (18/39)	
Modifying the types of study design	[32] [34] [49] [55]
Adding the eligibility criteria of study design	[24] [26] [27] [30] [31] [33] [35] [36] [40] [50] [51] [52]
Deleting the eligibility criteria of	[30] [31] [54] [56]

study design

Report characteristics (14/39)

Modifying the eligibility criteria of other study/report characteristics (sample size) [46]

Adding the eligibility criteria of other study/report characteristics (publication status, publication type, interested outcome) [24] [26] [27] [31] [33] [35] [36] [39] [48] [50] [51] [52]

Deleting the eligibility criteria of other study/report characteristics (sample size, publication status, publication type) [26] [41] [55]

Search (36/39)

Adding search process/method (search term, time range, database, filters, full search history, manual search of grey literature, re-run retrieval before the final analyses, etc.) [20] [22] [23] [24] [25] [26] [28] [30] [31] [32] [33] [34] [35] [36] [37] [38] [39] [40] [41] [42] [43] [44] [45] [46] [47] [48] [50] [51] [52] [53] [54] [55] [56] [58]

Deleting search process/method (full search history, re-run retrieval before the final analyses) [20] [39]

Modifying the method and thus reduce the comprehensiveness of search (reducing the databases, narrowing the time range) [27] [29] [30] [42] [50] [58]

Modifying the method and thus increase the comprehensiveness of search (increasing the databases, expanding the time range) [26] [27] [31] [32] [44] [48]

Quality (17/39)

Adding the literature selection process/method [22] [23] [27] [31] [32] [33] [34] [35] [36] [40] [41] [42] [51] [53] [56] [57] [58]

Quality assessment (15/39)

Adding the risk of bias assessment process/method [23] [26] [27] [29] [37] [38] [55]

Deleting the risk of bias assessment process/method [28] [30] [33] [44] [58]

Adding the assessed methodological [24] [35]

components

Deleting the assessed methodological components [33] [34] [56] [58]

Adding report how the risk of bias assessments are used in the data synthesis subsequently [27]

Modifying the tool used to assess the risk of bias [54]* [26] [34]

(35/39)

Adding the data extraction process/method [25] [27] [28] [29] [30] [31] [34] [38] [39] [41] [42] [49] [51] [53] [54] [57]

Deleting the data extraction process/method [26] [36]

Adding the list and definition of all variables for which data were sought or/and any assumptions/simplifications made [20] [22] [24] [26] [27] [28] [29] [30] [31] [32] [33] [35] [36] [39] [40] [42] [44] [45] [48] [49] [51] [52] [53] [54] [55] [56]

Deleting the list and definition of all variables for which data were sought or/and any assumptions/simplifications made [34] [43] [46] [47]

Adding the algorithm that the author used to select data from overlapping reports or/and any efforts they used to solve logical inconsistencies across reports [29] [37] [41] [42] [47] [53]

Modifying the algorithm that the author used to select data from overlapping reports [56]

a synthesis (30/39)

Adding the principal summary measures (risk ratio, difference in means, etc.)/the methods of handling data and combining results of studies (including measures of consistency for each meta-analysis)/the assessment of risk of bias that may affect the cumulative evidence (publication bias, selective reporting within studies, etc.)/the methods of additional analyses (sensitivity analyses, meta-regression, etc.) [21] [22] [24] [25] [26] [28] [29] [30] [31] [33] [36] [39] [42] [43] [45] [46] [47] [48] [51] [53] [54] [55] [56] [57] [58]

Deleting the principal summary measures (risk ratio, difference in means, etc.)/the methods of handling data and combining results of studies (including measures of consistency for each meta-analysis)/the assessment of risk of bias that may affect the cumulative evidence (publication bias, selective reporting within studies, etc.)/the methods of additional analyses (sensitivity analyses, meta-regression, etc.)

[21] [23] [35] [37]
[44] [53] [58]

Modifying the method of data synthesis

[49]

groups/subsets (25/39)

Adding the subgroups analysis

[21]
[24]
[28]
[29]
[42]
[46]
[47]
[48]
[51]
[53]

Deleting the subgroups analysis

[43]*

[20]
[26]
[27]
[31]
[36]
[37]
[44]
[49]
[54]
[55]
[56]

Modifying the subgroup analysis

[23]
[33]
[57]

*where the author provides an explanation for the change in published systematic review; PICO: participant(s), intervention(s), comparator(s), outcome(s)

Categories and impact of changes in each review

All of the systematic reviews included in this study (n=39) have undergone some changes, pertaining to a total of 50 change categories (in Table 1). The most rigorous systematic review[50] involved four

categories of changes, and the most varied systematic reviews[33] involved 14 categories of changes. The changes in 70% systematic reviews (n=27) have improved the quality as a whole (the number of improving being greater than the number of reducing and unclear). All changes to only one review were considered to improve the reporting/methodology quality (adding time range of search, adding list and definition of all variables for which data were sought, adding eligibility criteria of publication status and publication type), and remaining the 97% of systematic reviews (n=38) contained changes that were considered to reduce the methodology/reporting quality or that had an unclear impact. 85% of systematic reviews (n=33) contained at least one change that was considered to reduce the methodology/reporting quality. Furthermore, 85% of systematic reviews (n=33) contained at least one change whose impact was unclear. Characteristic of impact for all changes in each included review is shown in Fig.2.

Discussion

This study found that 100% of published non-Cochrane reviews (n=39) registered on PROSPERO underwent some changes against their protocols during the research process, pertaining to a total of 50 change categories. All changes to only a single review were considered to improve the reporting/methodology quality, and the remaining 97% of systematic reviews (n=38) contained changes that were considered to reduce the methodology/reporting quality or have an unclear impact on systematic reviews. Only 8% of included reviews (n=3) [22,43,54] provided explanations for individual changes in published full text. These results led us to ask whether the changes were necessary and how to further improve the transparency of non-Cochrane reviews.

The categories and impact of changes

Changes in the following sections, including search strategy, study selection, risk of bias assessment, data extraction, and data synthesis, primarily impacted the transparency, reproducibility, accuracy, and comprehensiveness of systematic reviews, thereby improving or reducing the methodology/reporting quality [5,6,18,19]. In the present study, changes in the “search strategy” section were the most significant (92%, n=36). Certain changes, such as adding manual search of grey literature or increasing search databases, may increase the comprehensiveness of search and thus improve the overall methodology quality of the review. However, when authors deleted manual search of grey literature or reduced search databases, the comprehensiveness of search could be affected and thus reduced the methodology quality. Other changes such as adding the time range for search could ensure that the literature searches were transparent and reproducible, which was important for assessing the strengths and weaknesses of a systematic review and re-running the literature searches when conducting an update review. Changes to titles primarily impacted the indexing and identification of systematic reviews[5]. For example, including the terms “systematic reviews” or “meta-analysis” in titles may improve indexing and identification of reviews. Moreover, the authors were always encouraged to use informative titles that made key information easily accessible to readers[5]. Thus, providing more key information (participants, intervention/exposure, comparator, outcome) about the scope of the reviews would improve the reporting quality of systematic reviews.

Changes in the following sections including review questions, participants, intervention/exposure, comparator, outcome, and study design consistently altered the scope of the systematic reviews and clinical applicability of the results, and generally, the impact on systematic reviews was not easy to detect. However, the retrospective nature of a systematic review would always put it at some risk of bias because of choices or judgments based on already existing knowledge of the evidence base[5,6,59]. 64% of reviews (n=25) exhibited changes in the “outcome” section. When authors make post-protocol modifications to review outcomes (that is, addition, removal, or re-prioritization) based on significance of outcome in the completed review, it can introduce bias into the review process, mislead readers and possibly affect patient care[60-65]. Moreover, through awareness of all study characteristics, systematic reviewers might be able to drive the results in different ways regarding participants (e.g., by applying age limits or rules when not all patients in a study met the inclusion criteria), intervention and comparison (e.g., omission of comparators which show an intervention less effective than the retained comparators), and definition of study designs (e.g., broadening of the types of studies included beyond randomized controlled trials alone to other potentially less-robust forms of comparison). For subgroup analysis, to avoid analyses revealing apparently compelling but in reality spurious subgroup differences, it should follow the principle specified in advance[66]. However, we found that 64% of reviews (n=25) exhibited changes in the “subgroup analysis” section. These changes could be a source of bias, especially without sensitivity analyses to test the effects of such changes.

Improving the transparency and its implementation

It is important to note that the impact of some of the changes may be later reflected when assessing the methodology quality/reporting quality/risk of bias of the systematic reviews in the future, whereas this may not be apparent for others[59]. For example, applying limits to databases or languages might be assessed negatively, resulting in a high risk of publication bias. However, modifying participants, intervention, comparison, outcomes, and subgroup analysis will generally be not easy to detect as potential sources of bias or manipulation. In the present study, we found that 85% of non-Cochrane systematic reviews (n=33) contained at least one category of change whose impact was unclear, and while 8% of reviews explained the reasons for individual changes, in these cases, the transparency of non-Cochrane systematic reviews was deemed inadequate. Recently, a study compared 80 non-Cochrane systematic reviews with their published protocols and also found that almost all systematic reviews (92.5%) differed from their protocols in at least one of the methodology-related “Preferred reporting items for systematic review and meta-analysis protocols” (PRISMA-P) items and their subcategories, while a mere 7% provided an explanation[67]. Additionally, an existing study investigated difference between non-Cochrane systematic reviews and their PROSPERO records and found that a third of systematic reviews changed or did not specify the primary outcome [63]. The existing researches showed that the differences between the published non-Cochrane reviews and their protocols were quite common. However, the explanations for the differences were rarely reported. Furthermore, a previous study [15] compared 47 completed Cochrane reviews with their published protocols using the “document compare” function in Microsoft Word and demonstrated that 91.5% of the reviews (n=43) contained major changes in methodology, and some of changes could be prone to influence by prior knowledge of results. Meanwhile,

at least 20% of Cochrane reviews have been found to make post-protocol modifications to review outcomes [59,64]. Cochrane reviews have since evolved to provide a dedicated section in which authors should report any changes made from the documented protocol.

Ideally, once a protocol is registered and published, the review should be performed in strict accordance with the protocol. This can effectively reduce the possibility of conscious or subconscious manipulation of inclusion criteria or outcome to reach a desired conclusion[7]. However, in some cases, valid reasons may exist for altering protocols while a review is being conducted. For example, legitimate modifications may extend the period of searches to include older or newer studies, broaden eligibility criteria that initially proved too narrow, or add analyses if the primary analyses suggest that such additional efforts are warranted. Registering a protocol is instrumental for developing good reviews, but it should not constitute an enforcement to paralyze any improvement. Authors should, however, describe the modifications and explain their rationale in the published review to strengthen the transparency of the review process[5,6].

The following solutions could be considered to strengthen the transparency of non-Cochrane reviews. First, we suggest PROSPERO takes some measures to encourage registrants to amend protocols (recording changes with explanations on PROSPERO). Second, we suggest that the PRISMA and MOOSE working group add a new item in an updated reporting checklist to guide the reviewers to report and explain the differences between protocols and systematic reviews. Meanwhile, readers or users of systematic reviews would be more easily made aware of the implications of reviews not following a-priori protocols by this measure. Third, the more effective measure to improve the transparency of systematic reviews could be regulations at the level of journals. We suggest that journals introduce a requirement in their author guidelines that any changes (with explanations) made to the protocols should be reported in a supplemental file of the published reviews. Editors or peer reviewers could compare manuscripts of systematic reviews with protocols and check back to confirm.

The strengths and limitations of this study

This is the first study to compare non-Cochrane systematic reviews with their protocols on PROSPERO specifically regarding differences in all methodology-related sections, as opposed to only changes in predefined outcome. We identified the changes in all compared methodology-related sections and evaluated their impact on reporting/methodology quality of systematic reviews using reliable tools (PRISMA/MOOSE and AMSTAR2). Furthermore, we created the change categories and quantified the characteristic of impact for all changes in each included review and each compared methodology-related section. Our results therefore represent a precise analysis of the differences in the methods between non-Cochrane systematic reviews and their protocols.

Certain limitations of our study must be acknowledged. First, we identified published non-Cochrane systematic reviews through the final publication details in PROSPERO records. It is therefore possible that the reviews could have been missed if the authors did not update this information. Second, due to limited resources, we did not verify these changes and their reasons with authors. Our comparison only based on

the reporting of the systematic reviews and their protocols, therefore leaving the possibility that the changes may not reflect “the truth” as experienced by the authors. For example, PROSPERO’s word limits on each of the record entries may explain why more details were submitted in published full text rather than in protocols. Additionally, Journals limits and specifications on reporting may explain why authors changed their protocols in some cases. Third, the generalizability of our results was only limited to the differences between the non-Cochrane systematic reviews and the latest version of protocols registered on PROSPERO. Partial non-Cochrane review protocols recorded on PROSPERO would also be published in peer-reviewed journals, but we did not identify whether a published one existed and whether the changes were highlighted in it.

Implications for future research

Future research should focus on the reporting quality of the review protocols registered on PROSPERO. The registry entry itself provides readers with a reference to compare against complete reviews, to examine for reporting biases[59]. Thus, the reporting quality will affect the judgment of the differences between the protocol and the full text, and therefore affect the transparency of the systematic reviews. Based on our results, we have some concern over the reporting quality of PROSPERO's protocol. During the process of comparison, we found that many protocols consisted of limited key information, such as search strategy, participants, interventions, comparators, and outcomes. Alarming, key information was often absent, even for mandatory fields such as study selection, data extraction, risk of bias assessment, and strategy for data synthesis. These absence may explain the vast improvement of included systematic reviews. However, the reporting issue of protocols could rarely be explained by PROSPERO’s word limits on each of the record entries. Furthermore, key information error was found in one review protocol (confusing the exposure and outcome[24]). We believe it’s also necessary to verify these changes, as well as investigate the reasons through correspondence with the authors. Moreover, it is interesting to investigate how many PROSRERO records have been published in peer-reviewed journals, and whether two versions of protocol exist differences.

Conclusions

Changes between the non-Cochrane systematic reviews and their protocols recorded on PROSPERO were widespread. “Search strategy”, “data extraction”, “data synthesis”, “outcome”, and “subgroup analysis” all showed significant changes. Some of the changes reduced the methodology or reporting quality of systematic reviews or had an unclear impact. Measures should be taken to further improve the transparency of the non-Cochrane systematic reviews. Adding new item in updated PRISMA and MOOSE to guide reporting and explaining any changes, as well as advising peer reviewers (and editors) to check the reviews against the protocols are two suggested fundamental solutions.

Abbreviations

PROSPERO: International prospective register of systematic reviews; PRISMA: Preferred reporting items for systematic review and meta-analysis; PRISMA-P: Preferred reporting items for systematic review and meta-analysis protocols; MOOSE: Meta-analysis of Observational Studies in Epidemiology; AMSTAR-2: a critical appraisal tool for systematic reviews that include randomized or non-randomized studies of healthcare interventions, or both; PICO: participant(s), intervention(s), comparator(s), outcome(s).

Declarations

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

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Authors' contributions

BM planned and designed the research; K-YH, Z-ZS and Y-BJ tested the feasibility of the study; K-YH, TZ, and W-YZ extract data; K-YH and QZ identify the categories and impact of change. YM, AW, and GT performed the statistical analysis; M-YJ and J-SWK proofread the language; K-YH wrote the manuscript; all authors approved the final version of the manuscript.

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Competing interests

The author declare that they have no competing interests.

References

1. Askie L, Offringa M. Systematic reviews and meta-analysis. *Semin Fetal Neonatal Med.* 2015; 20(6): 403-9.

2. Patsopoulos NA, Analatos AA, Ioannidis JPA. Relative Citation Impact of Various Study Designs in the Health Sciences. *JAMA*. 2005; 293(19): 2362–2366.
3. Page MJ, Shamseer L, Altman DG, Tetzlaff J, Sampson M, Tricco AC, Catalá-López F, Li L, Reid EK, Sarkis-Onofre R, Moher D. Epidemiology and Reporting Characteristics of Systematic Reviews of Biomedical Research: A Cross-Sectional Study. *PLoS Med*. 2016; 13(5): e1002028.
4. Chavalarias D, Ioannidis JP. Science mapping analysis characterizes 235 biases in biomedical research. *J Clin Epidemiol*. 2010; 63(11): 1205-15.
5. Liberati A, Altman DG, Tetzlaff J, et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate healthcare interventions: explanation and elaboration. *BMJ*. 2009; 339: b2700.
6. Higgins JPT, Thomas J, Chandler J, Cumpston M, Li T, Page MJ, Welch VA (editors). *Cochrane Handbook for Systematic Reviews of Interventions* version 6.0 (updated July 2019). Cochrane, 2019.
7. Stewart L, Moher D, Shekelle P. Why prospective registration of systematic reviews makes sense. *Syst Rev*. 2012; 1: 7.
8. Ge L, Tian JH, Li YN, Pan JX, Li G, Wei D, Xing X, Pan B, Chen YL, Song FJ, Yang KH. Association between prospective registration and overall reporting and methodological quality of systematic reviews: a meta-epidemiological study. *J Clin Epidemiol*. 2018 Jan;93:45-55.
9. Petticrew M, Wilson P, Wright K, Song F. Quality of Cochrane reviews. Quality of Cochrane reviews is better than that of non-Cochrane reviews. *BMJ*. 2002; 324(7336): 545.
10. M. Moseley, M.R. Elkins, R.D. Herbert, C.G. Maher, C. Sherrington. Cochrane reviews used more rigorous methods than non-Cochrane reviews: survey of systematic reviews in physiotherapy. *J Clin Epidemiol*. 2009; 62:1021-1030.
11. Booth A, Clarke M, Dooley G, et al. The nuts and bolts of PROSPERO: an international prospective register of systematic reviews. *Syst Rev*. 2012; 1: 2.
12. Booth A, Clarke M, Gherzi D, Moher D, Petticrew M, Stewart L. An international registry of systematic-review protocols. 2011; 377: 108-9.
13. International prospective register of systematic reviews. 2019. <https://www.crd.york.ac.uk/PROSPERO/#guidancenotes>. Accessed 5 February 2019.
14. Booth A, Clarke M, Gherzi D, Moher D, Petticrew M, Stewart L. Establishing a minimum dataset for prospective registration of systematic reviews: an international consultation. *PLoS One*. 2011; 6(11): e27319.
15. Silagy CA, Middleton P, Hopewell S. Publishing Protocols of Systematic Reviews: Comparing What Was Done to What Was Planned. *JAMA*. 2002; 287(21): 2831-2834.
16. International prospective register of systematic reviews. 2019. <https://www.crd.york.ac.uk/PROSPERO/#searchadvanced>. Accessed 14 August 2019.
17. International prospective register of systematic reviews. 2019. <https://www.crd.york.ac.uk/PROSPERO/#aboutregpage>. Accessed 1 February 2019.

18. Stroup DF, Berlin JA, Morton SC, et al. Meta-analysis of Observational Studies in Epidemiology: A Proposal for Reporting. *JAMA*. 2000;283(15):2008–2012.
19. Shea BJ, Reeves BC, Wells G, et al. AMSTAR 2: a critical appraisal tool for systematic reviews that include randomized or non-randomized studies of healthcare interventions, or both. *BMJ*. 2017;358:j4008. Published 2017 Sep 21.
20. Li XX, Huang XF, Bai CF, Qin DL, Cao SS, Mei QB, Ye Y, Wu JM. Efficacy and Safety of Teneclisiptin in Patients With Type 2 Diabetes Mellitus: A Systematic Review and Meta-Analysis of Randomized Controlled Trials. *Front Pharmacol*. 2018; 9: 449.
21. Silva Neto LGR, Santos Neto JED, Bueno NB, de Oliveira SL, Ataíde TDR. Effects of iron supplementation versus dietary iron on the nutritional iron status: Systematic review with meta-analysis of randomized controlled trials. *Crit Rev Food Sci Nutr*. 2018; 3: 1-9.
22. Ma WQ, Sun XJ, Wang Y, Han XQ, Zhu Y, Liu NF. Does body mass index truly affect mortality and cardiovascular outcomes in patients after coronary revascularization with percutaneous coronary intervention or coronary artery bypass graft? A systematic review and network meta-analysis. *Obes Rev*. 2018; 19(9): 1236-1247.
23. Lau Y, Nyoe RSS, Wong SN, Ab Hamid ZB, Leong BS, Lau ST. Effectiveness of digital resuscitation training in improving knowledge and skills: A systematic review and meta-analysis of randomized controlled trials. *Resuscitation*. 2018; 131: 14-23.
24. Mantovani A, Nascimbeni F, Lonardo A, Zoppini G, Bonora E, Mantzoros C.S, Targher G. Association between Primary Hypothyroidism and Nonalcoholic Fatty Liver Disease: A Systematic Review and Meta-Analysis. *Thyroid*. 2018; 28(10): 1270-1284.
25. Lattanzi S, Brigo F, Cagnetti C, Di Napoli M, Silvestrini M. Patent Foramen Ovale and Cryptogenic Stroke or Transient Ischemic Attack: To Close or Not to Close? A Systematic Review and Meta-Analysis. *Cerebrovasc Dis*. 2018; 45: 193-203.
26. Fernanda WM, Fernanda MS, Gilberto M, Saman W, Eliete NSG, Elena RCR. Maté consumption association with upper aerodigestive tract cancers: A systematic review and meta-analysis. *Oral Oncology*. 2018; 82: 37-47.
27. Al-Boloushi Z, López-Royo M.P, Arian M, Gómez-Trullén E.M, Herrero P. Minimally invasive non-surgical management of plantar fasciitis: A systematic review. *Journal of Bodywork and Movement Therapies*. 2019; 23(1): 122-137.
28. Bolfi F, Neves AF, Boguszewski CL, Nunes-Nogueira VS. Mortality in acromegaly decreased in the last decade: a systematic review and meta-analysis. *Eur J Endocrinol*. 2018; 179(1): 59-71.
29. Ramos-García P, González-Moles MÁ, González-Ruiz L, Ruiz-Ávila I, Ayén Á, Gil-Montoya JA. Prognostic and clinicopathological significance of cyclin D1 expression in oral squamous cell carcinoma: A systematic review and meta-analysis. *Oral Oncology*. 2018; 83: 96-106.
30. Sansone A, Cignarelli A, Sansone M, et al. Serum Homocysteine Levels in Men with and without Erectile Dysfunction: A Systematic Review and Meta-Analysis. *Int J Endocrinol*. 2018; 2018: 7424792.

31. Tsai TY, Kuo CY, Huang YC. Serum homocysteine, folate, and vitamin B12 levels in patients with vitiligo and their potential roles as disease activity biomarkers: A systematic review and meta-analysis. *J Am Acad Dermatol.* 2019; 80(3): 646-654.e5.
32. Kunutsor SK, Beswick AD, Whitehouse MR, Blom AW. Systematic review of risk prediction scores for venous thromboembolism following joint replacement. *Thromb Res.* 2018; 168: 148-155.
33. Gottlieb M, DeMott JM, Hallock M, Peksa GD. Systemic Antibiotics for the Treatment of Skin and Soft Tissue Abscesses: A Systematic Review and Meta-Analysis. *Ann Emerg Med.* 2019; 73(1): 8-16.
34. Mikhail M, Wormald JCR, Thurley N, Riley N, Dean B. Therapeutic interventions for acute complete ruptures of the ulnar collateral ligament of the thumb: a systematic review. *F1000Res.* 2018; 7: 714.
35. Al-Maweri SA, Kalakonda B, AlAizari NA, Al-Soneidar WA, Ashraf S, Abdulrab S, Al-Mawri ES. Efficacy of low-level laser therapy in management of recurrent herpes labialis: a systematic review. *Lasers Med Sci.* 2018; 33(7): 1423-1430.
36. CKunutsor SK, Seidu S, Khunti K. Depression, antidepressant use, and risk of venous thromboembolism: systematic review and meta-analysis of published observational evidence. *Ann Med.* 2018; 50(6): 529-537.
37. Betzel B, Drenth JPH, Siersema PD. Adverse events of the duodenal-jejunal bypass liner: a systematic review. *Obes Surg.* 2018; 28(11): 3669-3677.
38. Le J, Dorstyn DS, Mpofu E, Prior E, Tully PJ. Health-related quality of life in coronary heart disease: a systematic review and meta-analysis mapped against the International Classification of Functioning, Disability and Health. *Qual Life Res.* 2018; 27(10): 2491-2503.
39. Zhang YS, Weng WY, Xie BC, Meng Y, Hao YH, Liang YM, Zhou ZK. Glucagon-like peptide-1 receptor agonists and fracture risk: a network meta-analysis of randomized clinical trials. *Osteoporos Int.* 2018; 29(12): 2639-2644.
40. Huang SJ, Nalos M, Smith L, Rajamani A, McLean AS. The use of echocardiographic indices in defining and assessing right ventricular systolic function in critical care research. *Intensive Care Med.* 2018; 44(6): 868-883.
41. Han S, Woo S, Suh CH, Kim YJ, Oh JS, Lee JJ. A systematic review of the prognostic value of texture analysis in 18F-FDG PET in lung cancer. *Ann Nucl Med.* 2018; 32(9): 602-610.
42. Li X, Qie S, Wang X, Zheng Y, Liu Y, Liu G. The safety and efficacy of once-weekly glucagon-like peptide-1 receptor agonist semaglutide in patients with type 2 diabetes mellitus: a systemic review and meta-analysis. *Endocrine.* 2018; 62(3): 535-545.
43. Sathianathan NJ, Butaney M, Konety BR. The utility of PET-based imaging for prostate cancer biochemical recurrence: a systematic review and meta-analysis. *World J Urol.* 2018; 12.
44. Mummadi SR, Mishra R. Effectiveness of provider price display in computerized physician order entry (CPOE) on healthcare quality: a systematic review. *J Am Med Inform Assoc.* 2018; 25: 1228-1239.
45. Sadeghirad B, Morgan RL, Zeraatkar D, Zea AM, Couban R, Johnston BC, Florez ID. Human and Bovine Colostrum for Prevention of Necrotizing Enterocolitis: A Meta-analysis. *Pediatrics.* 2018; 142:

e20180767.

46. Han S, Suh CH, Woo S, Kim YJ, Lee JJ. Performance of 68Ga-DOTA-Conjugated Somatostatin Receptor Targeting Peptide PET in Detection of Pheochromocytoma and Paraganglioma: A Systematic Review and Meta-Analysis. *J Nucl Med*. 2018 Jul 20. pii: jnumed.118.211706.
47. Kojima Gotaro. Frailty Defined by FRAIL Scale as a Predictor of Mortality: A Systematic Review and Meta-analysis. *JAMDA*. 2018; 19(6): 480-483.
48. Shravya Govindappagari, Richard M. Burwick. Treatment of Iron Deficiency Anemia in Pregnancy with Intravenous versus Oral Iron: Systematic Review and Meta-Analysis. *Amer J Perinatol*. 2018; 131: 3-4.
49. Shinozaki S, Kobayashi Y, Hayashi Y, Sakamoto H, Lefor AK, Yamamoto H. Efficacy and safety of cold versus hot snare polypectomy for resecting small colorectal polyps: Systematic review and meta-analysis. *Dig Endosc*. 2018; 30(5): 592-599.
50. McGregor G, Powell R, Finnegan S, Nichols S, Underwood M. Exercise rehabilitation programmes for pulmonary hypertension: a systematic review of intervention components and reporting quality. *BMJ Open Sport Exerc Med*. 2018; 4(1): e000400.
51. Dai W, Liu A, Kaminga AC, Deng J, Lai Z, Wen SW. Prevalence of Posttraumatic Stress Disorder among Children and Adolescents following Road Traffic Accidents: A Meta-Analysis. *Can J Psychiatry*. 2018; 6: 706743718792194.
52. Mohamad M. Saab, Martin Davoren, Aileen Murphy, David Murphy, Eoghan Cooke, Margaret Landers, Serena Fitzgerald, Noel Richardson, Michael Rovito, Christian Von Wagner, Mike Murphy, Darren Dahly, Josephine Hegarty. Promoting men's awareness, self-examination, and help-seeking for testicular disorders: a systematic review of interventions. *HRB Open Research*. 2018; 1: 16.
53. Kojima G. Quick and Simple FRAIL Scale Predicts Incident Activities of Daily Living (ADL) and Instrumental ADL (IADL) Disabilities: A Systematic Review and Meta-analysis. *J Am Med Dir Assoc*. 2018; 19(12): 1063-1068.
54. Palui R, Sahoo J, Kamalanathan S, Kar SS, Selvarajan S, Durgina H. Effect of cabergoline monotherapy in Cushing's disease: an individual participant data meta-analysis. *J Endocrinol Invest*. 2018; 41(12): 1445-1455.
55. Tóth B, Hegyi P, Lantos T, Szakács Z, Kerémi B, Varga G, Tenk J, Pétervári E, Balaskó M, Rumbus Z, Rakonczay Z, Bálint ER, Kiss T, Csupor D. The Efficacy of Saffron in the Treatment of Mild to Moderate Depression: A Meta-analysis. *Planta Med*. 2019; 85(1): 24-31.
56. Mari A, Kimura S, Foerster B, Abufaraj M, D'Andrea D, Gust KM, Shariat SF. A systematic review and meta-analysis of lympho-vascular invasion in patients treated with radical cystectomy for bladder cancer. *Urol Oncol*. 2018; 36: 293-305.
57. Islam MA, Alam F, Cavestro C, Calcii C, Sasongko TH, Levy RA, Gan SH. Antiphospholipid antibodies in epilepsy: A systematic review and meta-analysis. *Autoimmun Rev*. 2018; 17(8): 755-767.
58. González-Bueso V, Santamaría JJ, Fernández D, Merino L, Montero E, Ribas J. Association between Internet Gaming Disorder or Pathological Video-Game Use and Comorbid Psychopathology: A

- Comprehensive Review. *Int J Environ Res Public Health*. 2018; 15(4): 668.
59. Shamseer Larissa, Moher David, Clarke Mike, Gherzi Davina, Liberati Alessandro, Petticrew Mark et al. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015: elaboration and explanation. *BMJ*. 2015; 349 :g7647
 60. Pieper D, Allers K. Differences between protocols for randomized controlled trials and systematic reviews. *J Clin Epidemiol*. 2018 Jun;98:144-145.
 61. Dwan K, Kirkham JJ, Williamson PR, Gamble C. Selective reporting of outcomes in randomized controlled trials in systematic reviews of cystic fibrosis. *BMJ Open*. 2013; 3(6): e002709.
 62. Kirkham JJ, Altman DG, Williamson PR. Bias due to changes in specified outcomes during the systematic review process. *PLoS One*. 2010; 5(3): e9810.
 63. Tricco AC, Cogo E, Page MJ, Polisena J, Booth A, Dwan K, MacDonald H, Clifford TJ, Stewart LA, Straus SE, Moher D. A third of systematic reviews changed or did not specify the primary outcome: a PROSPERO register study. *J Clin Epidemiol*. 2016; 79: 46-54.
 64. Page MJ, McKenzie JE, Kirkham J, Dwan K, Kramer S, Green S, Forbes A. Bias due to selective inclusion and reporting of outcomes and analyses in systematic reviews of randomized trials of healthcare interventions. *Cochrane Database Syst Rev*. 2014; 10: MR000035.
 65. Kirkham JJ, Dwan KM, Altman DG, Gamble C, Dodd S, Smyth R, Williamson PR. The impact of outcome reporting bias in randomized controlled trials on a cohort of systematic reviews. *BMJ*. 2010; 340: c365.
 66. Sun X, Ioannidis JPA, Agoritsas T, Alba AC, Guyatt G. How to Use a Subgroup Analysis: Users' Guide to the Medical Literature. *JAMA*. 2014;311(4):405–411.
 67. Koensgen N, Rombey T, Allers K, Mathes T, Hoffmann F, Pieper D. Comparison of non-Cochrane systematic reviews and their published protocols: differences occurred frequently but were seldom explained. *J Clin Epidemiol*. 2019 Jun;110:34-41.

Figures

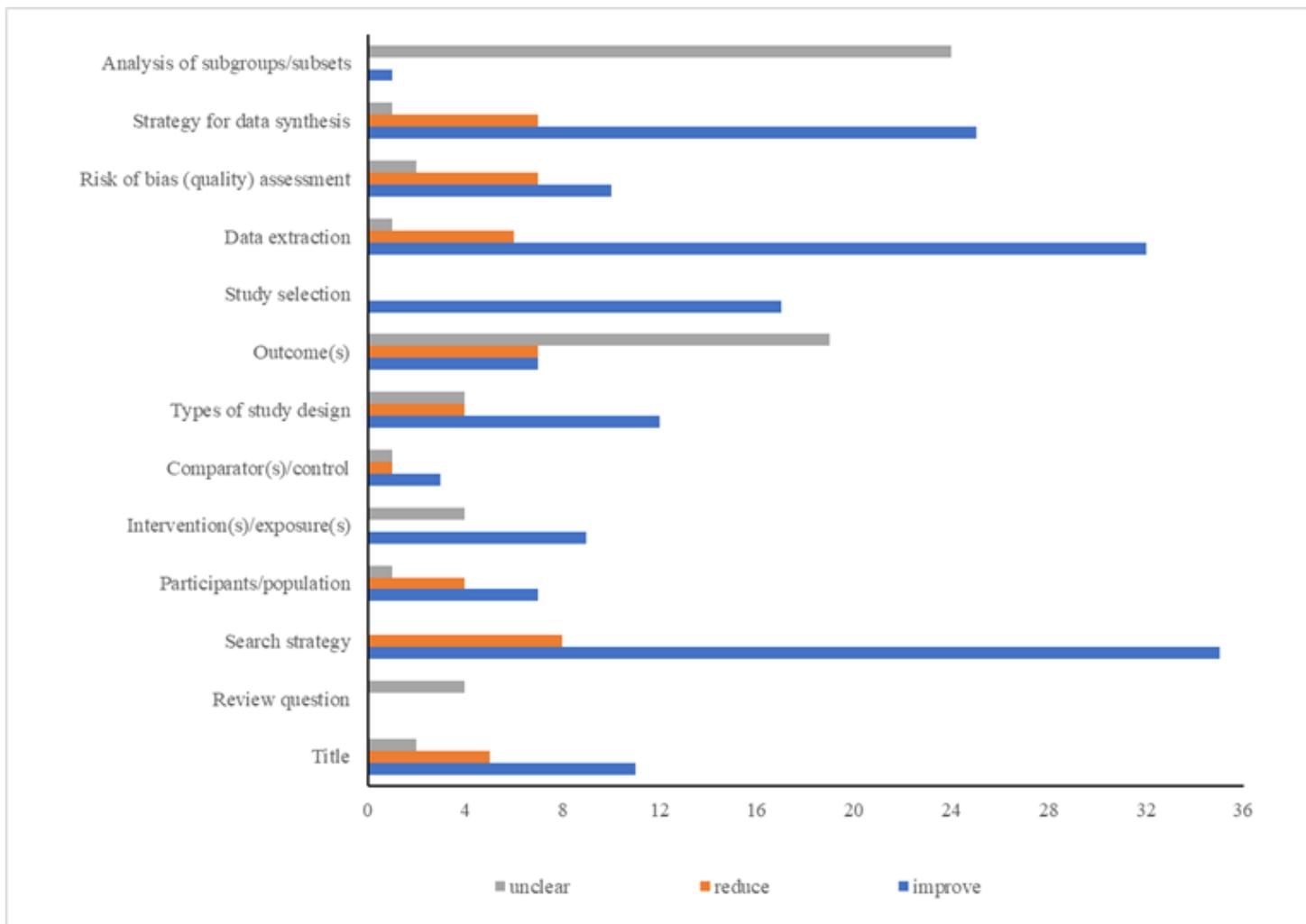


Figure 1

Categories and impact of changes in each review

All of the systematic reviews included in this study (n=39) have undergone some changes, pertaining to a total of 50 change categories (in Table 1). The most rigorous systematic review[50] involved four categories of changes, and the most varied systematic reviews[33] involved 14 categories of changes. The changes in 70% systematic reviews (n=27) have improved the quality as a whole (the number of improving being greater than the number of reducing and unclear). All changes to only one review were considered to improve the reporting/methodology quality (adding time range of search, adding list and definition of all variables for which data were sought, adding eligibility criteria of publication status and publication type), and remaining the 97% of systematic reviews (n=38) contained changes that were considered to reduce the methodology/reporting quality or that had an unclear impact. 85% of systematic reviews (n=33) contained at least one change that was considered to reduce the methodology/reporting quality. Furthermore, 85% of systematic reviews (n=33) contained at least one change whose impact was unclear. Characteristic of impact for all changes in each included review is shown in Fig.2.

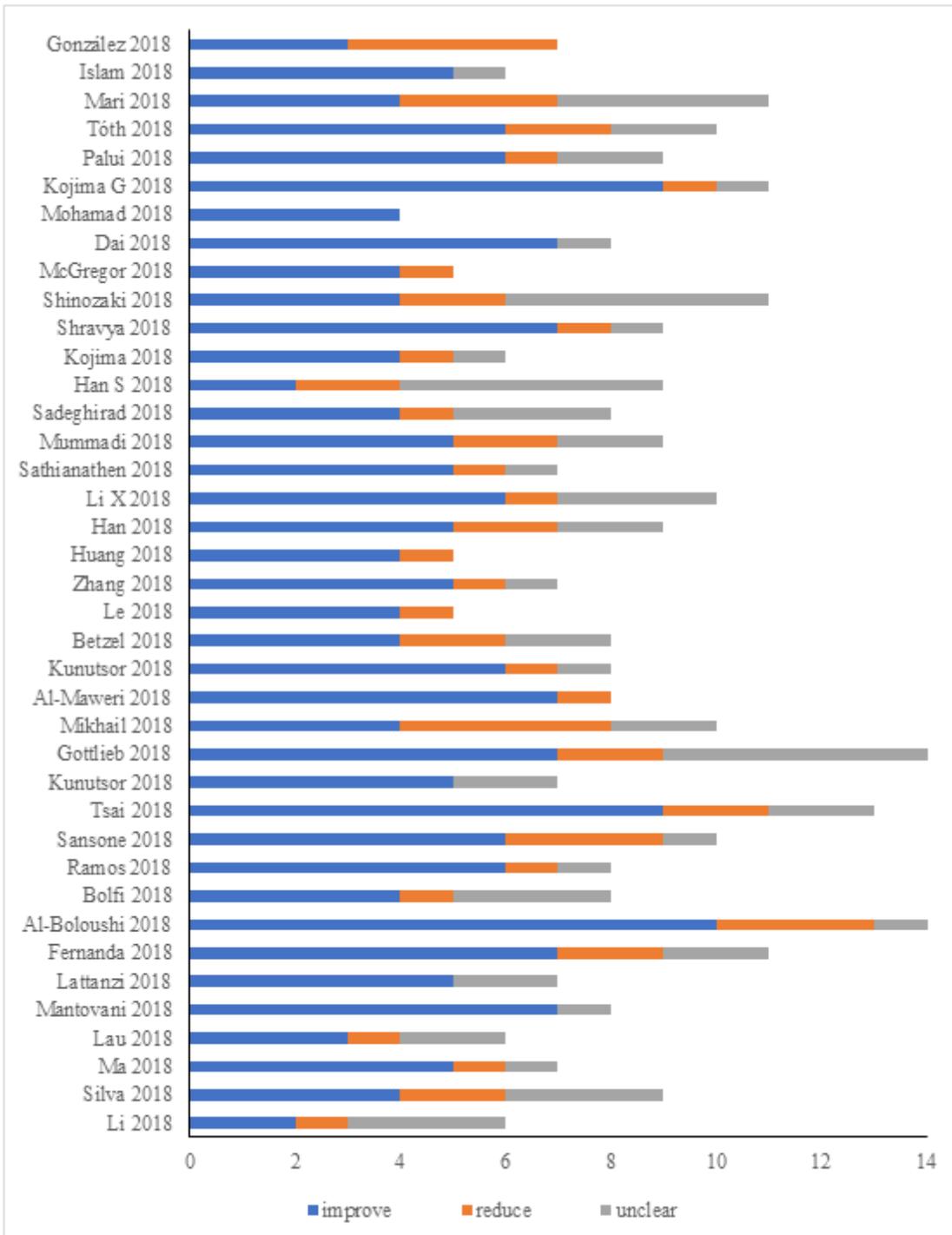


Figure 2

Characteristic of impact for all changes (x axis) in each included review (y axis)

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