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

Kaiyan Hu
Lanzhou University
Ting Zhang
Lanzhou University
Weiyi Zhang
Lanzhou University
Qi Zhou
Lanzhou University
Joey S.W. Kwong
Chinese University of Hong Kong
Yuxia Ma
Lanzhou University
Yanbiao Jiang
Lanzhou University
Zhizhong Shang
Lanzhou University
Anhu Wu
Lanzhou University
Gongcai Tao
Lanzhou University
Kehu Yang
Lanzhou University
Bin Ma (kittymb2017@163.com)

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Abstract

Background: Protocols of systematic reviews allow for planning and documentation of review methods, and thus improve the transparency of reviews process. However, pre-registered a protocol is not enough, the author also need to follow it. PROSPERO is an open-access online facility for the registration of non-Cochrane systematic reviews. The purpose of our research is to determined what changed were made between non-Cochrane reviews and their protocols in PROSPERO and how likely these changes impacted the quality of systematic review.

Method: In this retrospective comparative study we electronically searched for protocols and their corresponding systematic reviews in the PROSPERO platform that were “completed and published” from January to December, 2018. Two reviewers independently identified and classified changes between the protocols and systematic reviews then evaluated the impact (improve/reduce/unclear)of these change on the reporting/methodology quality of reviews. Frequency (n), percentage (%) were used to analyze the number of changes categorically in each review and the distribution of different impact caused by these changes.

Results: We identified 39 pre-registered protocols and their reviews, all of which exhibited alterations. All changes to only one review are considered to improve the reporting/methodology quality, and remaining 97% of reviews (n=38) contain changes that are categorically considered to reduce the methodology/reporting quality or that have an unclear impact on reviews.

Conclusions: Differences between the non-Cochrane reviews and their protocols recorded in PROSPERO are widespread, and there have been many changes having an unclear impact on the quality of reviews. Guiding the author to report and explain the differences between protocol and reviews or even requiring authors to so at the level of journal are two fundamental solutions to further improve the transparency of the non-Cochrane reviews.

Background

Systematic reviews critically evaluate existing evidence with the aim of answering specific clinical questions, thereby enabling the formulation of clinical recommendations and guidance for future research[1, 2]. Systematic review is the cornerstone of evidence-based health care and is widely promoted as providing the best evidence for informed decision-making[3]. Because of 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, provided a registration platform and published protocols for systematic review with an aim 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 produce a minority of published 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 quality 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 facility for the registration of non-Cochrane systematic reviews. Registration in PROSPERO involves the 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 reviews and the previously published 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, such as addition or deletion of outcomes. Up to December 31th, 2018, there were a total of 45,638 systematic reviews registered in PROSPERO, among which 3,976 were published[16]. To our knowledge, no study to date has compared the texts of published protocols in PROSPERO with their corresponding systematic reviews. In addition, unlike the Cochrane library's rigorous assessment of registered protocols, PROSPERO has no quality assessment or peer review for submitted protocols[17]. As such, the objective of our review was to compare published non-Cochrane reviews with their pre-registered protocols in PROSPERO to determine which changes were made in methodology-related sections and how likely these changes impacted the quality of systematic review.

Methods

The search for protocols and reviews

We sought to identify all completed systematic reviews of interventions and observations that were pre-registered in PROSPERO. The search strategy was developed and executed in January 2019. We electronically searched for all non-Cochrane protocols in the PROSPERO platform that were “completed and published” between January 1 and December 31 of 2018. These records most often included a citation and link to the final publication. For invalid citations or links, we manually searched for the reviews in open databases (PubMed, Embase, and Web of Science) using the title of final published review. After the identification of published reviews, we downloaded the latest version of the protocol and corresponding review into a folder. The reviews of non-clinical studies were excluded. Completed reviews not published in English were also excluded, due to resource limitations. In cases where we found two protocols registered for the same published review, we contacted the authors for clarity on which protocol should be considered the final corresponding protocol.

Assessment

For each included review, two reviewers (Kaiyan Hu and Ting Zhang) independently assessed whether a change had occurred in each compared methodology-related section. For the purpose of our research, we did not consider alterations in tense, abbreviations, style, or wording as a change, as these changes neither altered the substance or meaning of a section, nor did they alter the interpretation of anyone attempting to replicate the review. Any other change that altered the substance or meaning of a section, or would have altered the interpretation by someone seeking to replicate the review, was regarded as change. Any remaining doubts were resolved through discussion with the third reviewer (Bin Ma). Prior to the formal assessment, a random sample of ten included systematic reviews was assessed by the two reviewers (Kaiyan Hu and Ting Zhang) simultaneously, and the assessment did not commence until high agreement (> 90%) was achieved.

For any difference between a systematic review and its protocol, two authors (Kaiyan Hu and Ting Zhang) independently determined if the differences had been reported and explained in the published reviews or amendatory

protocols. Discrepancies were resolved through discussion until consensus was reached by both authors as to whether the reviews “explained” the differences sufficiently.

Data extraction

Data extraction tables were created in Microsoft Office Word 2016 software. The data were extracted independently and cross-checked by the two reviewers (Kaiyan Hu and Ting Zhang), and disagreements were discussed and resolved with the third reviewer (Bin Ma). The sections of focus, where changes had occurred from both protocols and reviews, were abstracted in the created table“Each change in the systematic reviews compared to their protocols”. The reviewers assessed whether there had been changes in any of the following 13 methodology-related sections: title, review question, search strategy, participants/population, intervention(s)/exposure(s), comparator(s)/control, types of study to be included, main 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 all mandatory registration entries required by PROSPERO.

Identification the categories and impact of change

For changes in each methodology-related section, two reviewers (Kaiyan Hu and Qi Zhou) independently defined the type of changes (e.g.: adding/deleting/modifying) and then, according to the corresponding items or subcategories in “Preferred reporting items for systematic review and meta-analysis ”(PRISMA)[5] or “Meta-analysis of Observational Studies in Epidemiology”(MOOSE)[18] and “a critical appraisal tool for systematic reviews that include randomized or non-randomized studies of healthcare interventions, or both” (AMSTRA2)[19], they evaluated the impact of these changes as reducing or improving the methodology and reporting quality of systematic reviews. For the reporting of any contents not mentioned in the current version of PRISMA/MOOSE, such as literature management software or statistical software, or methods to assess the strength of the evidence body, etc., any changes involved would be regarded as improving or reducing the quality of the reporting. We also judged the impact of changes based on the research background. For example, the author may add exclusion criteria to reduce confounders or increase comparability of the control group. Next, the type of change with the same impact in each section was generalized and summarized to form the final category of change. There are some changes, the nature of whose impact cannot be defined by improving or reducing the methodology or reporting quality, such as expending/narrowing/modifying review questions by changing eligibility criteria, adding or deleting outcome, upgrading or downgrading outcome, or adding or deleting subgroup analyses. If the author did not explain the rationality behind these types of changes in the published reviews or amendatory protocols, we evaluated the impact of these changes as “unclear.” However, if the author stated a valid explanation for the change, we defined the impact of these changes as improving the reporting quality. The two reviewers (Kaiyan Hu and Qi Zhou) cross-checked the evaluation results and discussed the differences with a third reviewer (Bin Ma).

Statistical methods

Microsoft Office Excel 2016 software was used for statistical analysis. Frequency (n), percentage (%) were used to analyze the number of changes categorically in each review and the distribution of different impact caused by these changes. A descriptive analysis of the types of changes and examples in each section was also conducted.

Results

Included studies

From January 1 to December 31 of 2018, 15,667 non-Cochrane protocol records were registered with PROSPERO, and 43 reviews were completed and published (Fig. 1). Of the 43 potentially relevant reviews, 2 were excluded because they were systematic reviews of non-clinical studies. There were two identical reviews corresponding to two different protocols (with the registration numbers CRD42018086539 and CRD42018084876). We contacted the author and determined with which protocol the review corresponded (Additional file 1). Additionally, there was a systematic review registered after the full text was published, which was also excluded as the purpose of this study was to compare published non-Cochrane reviews with their pre-registered protocols in PROSPERO. All excluded reviews are listed in Additional file 2. 39 systematic reviews[20–58] fulfilled the eligibility criteria and were subsequently included.

The result of comparison

All changes in the systematic reviews compared to their protocols were compiled (see Additional file 3). These changes involved all 13 compared methodology-related sections and all included systematic reviews.

During the process of comparison, we found that many published protocols consisted of very limited key information, such as participant, intervention/exposure, comparator, outcome, study design details. More alarmingly, key information was often absent even for mandatory fields such as search strategy, study selection, data extraction, risk of bias assessment, and strategy for data synthesis. Furthermore, key information errors were found in two review protocols, confusing the exposure and outcome subgroup leading to a lack of clarity[24, 27]. Other errors were discovered including the fact that protocols did not provide the details of the search strategy, despite the fact that the published review[34] stated explicitly that the detailed search strategy could be found in the protocol.

Categories and impact of changes in each section

The change categories in each section and their impact on the quality of systematic reviews were defined. Examples for each category as well as references reporting each example are presented in Table 1. 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 87% of reviews (n = 34) exhibiting changes in data extraction and 77% of reviews (n = 30) exhibiting changes in data synthesis. In addition, more than 71% reviews (n = 28) exhibited changes in the outcome section. The number of systematic reviews that improved the quality, reduced the quality, or had an unclear impact for each compared methodology-related section are shown in in Fig. 2.

Table 1

Categories and impact of changes (n = 39).

Section (Change amount/Total)	Categories of change	Improve the reporting/methodology quality	Reduce the reporting/methodology quality	Unclear (Having the potential risk of introducing bias)
Title (16/39)				
	Inclusion of the terms “systematic reviews” and “Meta-analysis” in the title	[33] [43] [49]		
	More accuracy key information (PICOS) about the scope of the reviews was provided	[21] [25] [31] [34] [38] [47] [49] [50]		
	Exclusion of the terms “systematic reviews” and ‘Meta-analysis” from review title		[40] [46]	
	The key information (PICOS) about the scope of the reviews was deleted		[45] [48] [55]	
	The key information (PICOS) about the scope of the reviews was changed			[46] [56]
Review question (5/39)				
	Modification of the review question by changing the intervention			[25]
	Narrowing the review question by deleting the exposures or interventions			[33] [46]
	Expanding the review question by considering safety in addition to efficacy			[49]
Eligibility criteria				
Participant (12/39)				
	Modifying the eligibility criteria of participant, like age, diagnosis			[31] [32] [34] [45] [49] [56]
	Adding the exclusion criteria of included participant to reduce confounders	[21] [24] [27] [48] [53] [57]		
Intervention(s)/exposure (s) (13/39)				

Section (Change amount/Total)	Categories of change	Improve the reporting/methodology quality	Reduce the reporting/methodology quality	Unclear (Having the potential risk of introducing bias)
	Modifying the intervention/exposure and thus changing the scope of review			[25] [33] [46]
	Modifying the eligibility criteria of intervention, like duration of treatment, drug dose, administration way			[21] [39] [45]
	Adding the exclusion criteria of intervention/exposure, like additional co-interventions and other Inapplicable interventions or exposures	[27] [41] [44] [55]		
	Adding the definitions/measures of exposure	[22]* [24] [30]		
Comparator(s)/control (4/39)				
	Modification the intervention of control group and thus changing the scope of review			[33] [35]
	Adding the inclusion/exclusion to increasing the comparability of the control group	[44] [57]		
Outcome (28/39)				
	Modifying the outcome			[28] [32] [33] [46] [56]
	Deleting the distinction between primary and secondary outcome			[20] [21] [41] [42] [45] [49]
	Adding/deleting primary or secondary outcome			[20] [21] [22] [23] [27] [28] [30] [31] [37] [41] [42] [43] [44] [45] [54]
	Adding the measures/definition of outcome	[25] [29] [37] [43] [53] [54] [55]		

Section (Change amount/Total)	Categories of change	Improve the reporting/methodology quality	Reduce the reporting/methodology quality	Unclear (Having the potential risk of introducing bias)
	Deleting the measures/definition of outcome		[22] [27] [34] [37] [38] [41] [49]	
Types of study to be included (18/39)				
	Modifying the study type and thus expanding/narrowing the scope of included studies			[30] [31] [32] [34] [49] [54] [55] [56]
	Adding exclusion criteria of some special study type, like conference abstract, review, case report, commentaries, editorials, etc. and improve the transparency of systematic reviews	[24] [26] [27] [31] [33] [35] [36] [40] [50] [51] [52]		
Others (7/39)				
	Adding inclusion/exclusion criteria that studies reported/didn't reported interested outcome and improve the transparency of systematic reviews (helping readers ascertain whether the systematic review may be biased as a consequence of selective reporting.)	[24] [27] [39] [48] [50]		
	Modifying the eligibility criteria, including sample size of included studies			[41] [46]
Search strategy (36/39)				
	Adding search term/language restriction/time range of retrieval/database/ filters of retrieval to increase research transparency and repeatability	[20] [23] [24] [25] [26] [28] [30] [31] [32] [33] [35] [36] [38] [40] [42] [43] [44] [45] [46] [47] [48] [51] [52] [53] [55]		

Section (Change amount/Total)	Categories of change	Improve the reporting/methodology quality	Reduce the reporting/methodology quality	Unclear (Having the potential risk of introducing bias)
	Deleting method to ensure the accuracy and comprehensiveness of retrieval, including reducing the database of retrieval, narrowing the time range for retrieval, deleting the re-run retrieval before the final analyses, deleting the manual search of grey literature etc.		[20] [21] [27] [29] [30] [42] [50] [55] [58]	
	Adding methods to ensure the accuracy and/or comprehensiveness of retrieval, including increasing the database of retrieval, expanding the time range for retrieval, adding the manual search of grey literature etc.	[22] [23] [25] [26] [27] [28] [31] [32] [33] [35] [37] [38] [39] [41] [44] [45] [47] [48] [51] [54] [56] [58]		
	Deleting search term/language restriction/time range of retrieval/ database of retrieval and thus reducing research transparency and repeatability		[39] [42] [56]	
Study selection (20/39)				
	Adding a description of the literature selection process/method and thus improve transparency/accuracy	[22] [23] [27] [28] [29] [31] [32] [33] [34] [35] [37] [40] [41] [42] [51] [53] [56] [57] [58]		
	Deleting a description of the literature selection process/method and thus reduce transparency/ accuracy		[36]	
Risk of bias (quality) assessment (17/39)				
	Adding the process/methods to ensure accuracy of assessment	[23] [26] [27] [29] [38] [55]		
	Deleting the process/methods to ensure accuracy of assessment		[28] [30] [33] [44] [58]	

Section (Change amount/Total)	Categories of change	Improve the reporting/methodology quality	Reduce the reporting/methodology quality	Unclear (Having the potential risk of introducing bias)
	Deleting the methodological components that they assessed		[33] [34] [56] [58]	
	Adding the methodological components that they assessed	[35]		
	Modifying the tool used to assess the risk of bias	[54]*		[26] [34]
	Adding the tool used to assess the risk of bias	[37] [52]		
	Adding description of how the strength of the body of evidence will be assessed (such as GRADE)	[26] [28] [52]		
	Adding report how the assessments of risk of bias are used subsequently in the data synthesis	[27]		
Data extraction (34/39)				
	Adding the data extraction process/method	[25] [27] [28] [29] [30] [31] [34] [39] [41] [42] [49] [51] [53] [54] [57]		
	Deleting the data extraction process/method		[26]	
	Adding the list and definition of all variables for which data were sought or any assumptions/simplifications made	[20] [22] [24] [26] [27] [28] [29] [30] [31] [32] [33] [35] [36] [39] [40] [42] [44] [45] [48] [49] [52] [53] [54] [55]		
	Deleting the list and definition of all variables for which data were sought or any assumptions/simplifications made		[34] [46] [47]	
	Modifying the list and definition of variables for which data were sought or any assumptions/simplifications made			[38] [43] [51]

Section (Change amount/Total)	Categories of change	Improve the reporting/methodology quality	Reduce the reporting/methodology quality	Unclear (Having the potential risk of introducing bias)
	Adding the algorithm that the author used to select data from overlapping reports and/or any efforts they used to solve logical inconsistencies across reports	[29]# [37] [42]# [47]# [41] [53]#		
	Modifying the algorithm that the author used to select data from overlapping reports			[56]#
Strategy for data synthesis (30/39)				
	Adding the principal summary measures (such as risk ratio, difference in means)/ 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 (such as publication bias, selective reporting within studies)/ the methods of additional analyses (such as sensitivity analyses, meta-regression)/ the tool of statistical analysis	[21] [22] [24] [25] [26] [28] [29] [30] [31] [33] [36] [39] [40] [42] [43] [45] [46] [47] [48] [51] [53] [54] [55] [56] [57] [58]		
	Deleting the principal summary measures (such as risk ratio, difference in means)/ 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 (such as publication bias, selective reporting within studies)/ the methods of additional analyses (such as sensitivity analyses, meta-regression)/the tool of statistical analysis		[21] [23] [35] [36] [37] [44] [53] [58]	
	Changing the method of combining results of studies			[40]

Section (Change amount/Total)	Categories of change	Improve the reporting/methodology quality	Reduce the reporting/methodology quality	Unclear (Having the potential risk of introducing bias)
Analysis of subgroups/subsets (14/39)				
	Adding the subgroups analysis			[21] [24] [28] [29] [42] [46] [47] [48] [51] [53]
	Deleting the subgroups analysis	[43]*		[20] [26] [31] [56] [37] [44] [45] [49] [54] [55]
	Deleting the original subgroup analysis and adding a new subgroup analysis			[23] [33] [38] [57]

# denotes a change occurring in the eligibility criteria section of the included systematic reviews; * denotes where the author provides a reasonable explanation for the change of corresponding categories in this systematic review.

The distribution of different impact for changes in each review

All of the systematic reviews included in this study have undergone some changes compared to their protocols. A minimally rigorous systematic review[50] involved four categories of changes, and the most varied systematic reviews[33] involved 14 categories of changes. The changes in 77% systematic reviews (n = 30) 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 are considered to improve the reporting/methodology quality, and remaining 97% of systematic reviews (n = 38) contain changes that are categorically considered to reduce the methodology/reporting quality or that have an unclear impact on systematic reviews. 77% of systematic reviews (n = 30) contain at least one change that is considered to reduce the methodology/reporting quality. 90% of systematic reviews (n = 35) contain at least one category of change whose impact on systematic review is unclear. The distribution of changes that improve the quality, reduce the quality, or have an unclear impact in each review is illustrated in Fig. 3.

Discussion

This study has demonstrated that 100% of published non-Cochrane reviews (n = 39) with a protocol in the PROSPERO underwent alterations during the research process, and these alterations involved all 13 compared method-related sections. All changes to only a single review were considered to improve the reporting/methodology quality, and the remaining 97% of systematic reviews (n = 38) contain changes that were considered to reduce the methodology/reporting quality or have an unclear impact on systematic reviews. Only 8% of the reviews analyzed included reviews (n = 3) [22, 43, 54] that provided reasonable explanations for individual changes in the published full

text. These results led us to ask whether these alterations were necessary and whether the value of the protocols that are registered in advance in PROSPERO warrants improvement in order to increase transparency.

The categories and impact of change

Changes in the following sections, including search strategy, study selection, risk of bias assessment, data extraction, and data synthesis, primarily impact the transparency, reproducibility, accuracy, and comprehensiveness of the systematic reviews, thereby improving or reducing the methodology/reporting quality of the reviews[5, 6, 18, 19]. For example, certain alterations to the search strategy, such as expanding the retrieval time range and increasing the retrieval databases, may increase the comprehensiveness of the search strategy and thus improve the overall methodology quality of the review. However, when authors reduce their search databases, narrow the time range of retrieval, and remove supplemental information, searches will affect the comprehensiveness of retrieval and thus reduce the methodology quality. Other alterations such as adding the time range for retrieval can ensure that the literature searches are transparent and reproducible, which is 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 impact the indexing and identification of systematic reviews[5]. For example, including the terms “systematic reviews” or “meta-analysis” may improve indexing and identification of reviews. Moreover, the authors are always encouraged to use informative titles that make key information easily accessible to readers[5]. Thus, providing more accuracy by specifying key information (participants, intervention/exposure, comparator, outcome, type of study) about the scope of the reviews would also improve the 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 generally, the impact on quality of reviews was not easy to detect. However, the retrospective nature of a systematic review will 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, 60]. For example, when authors make post-protocol modifications to review outcomes (that is, addition, removal, or reprioritization) based on significance of the outcome in the completed review, it can introduce bias into the review process, mislead readers and possibly affect patient care[59, 65]. Several studies have suggested that discrepant outcome reporting between protocols and published Cochrane/non-Cochrane reviews was fairly common and increased the likelihood of reporting statistically significant outcomes[61–64]. 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 of the systematic reviews), intervention and comparison (e.g., by applying duration of treatment limits or rules when not all intervention met the inclusion criteria of the systematic reviews), outcome (e.g., including their definition such as “using validated scales”) 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).

To avoid analyses revealing apparently compelling, but in reality spurious subgroup differences, from multiple post hoc analyses, subgroup analysis should follow the principle specified in advance[66]. Therefore, changing the subgroup analysis 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 methodological/reporting quality and/or 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 bias in this particular area. Definitions of participants, intervention, comparison, outcomes, study design, and subgroup analysis will generally be not easy to detect as potential sources of bias or manipulation. We found that in 90% of non-Cochrane systematic reviews with a pre-registered protocol in PROSPERO, at least one category of the changes had an impact on the quality of reviews that was unclear, and while 8% of reviews explained the reasons for these 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 methods-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]. Other existing empirical studies investigated difference between non-Cochrane systematic reviews and their PROSPERO records and found that discrepancy in outcome reporting between protocols and published reviews was fairly common[61–64]. Therefore, existing research shows that the differences between the published non-Cochrane reviews and their protocols are indeed quite common, though the reasons for the differences are rarely reported.

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 reduce bias and strengthen transparency of the production process[5, 6].

The responsibility of authors to follow their protocols or to clearly explain and rationalize any changes should be highlighted further. Systematic review authors should be encouraged to amend their protocols, and record all changes made with explanation in PROSPERO. We also suggest adding a new item to PRISMA and MOOSE in the future in order to provide the author the ability to report the differences between protocols and the systematic reviews with sufficient explanation. Meanwhile, readers or users of systematic reviews would be more easily made aware of the implications of reviews not following a-priori protocols. In the future, more effective measures to improve the transparency of systematic reviews could include provisions where journals request of the author in their guidelines that any changes (and appropriate reasons) made to the original research protocol are provided in an appendix of the published review. Editors or peer reviewers could compare manuscripts for systematic reviews with their protocols and check back confirm with the authors whether changes have not been reported or explained. The transparency of systematic reviews also requires regulation at a higher level, such as the International Medical Journal Editors' Committee (ICJE), to promote the publication of uniform and standardized biomedical science journals.

The strengths and limitations of this study

This is the first study to compare non-Cochrane systematic reviews with protocols in PROSPERO specifically regarding differences in all methodology-related sections, as opposed to only changes in predefined outcome. We summarized all categories of changes between non-Cochrane systematic reviews (no limitation of intervention/observation) and

their pre-registered protocol in PROSPERO and evaluated the impact of all these categories of changes on the reporting/methodology quality of systematic reviews using reliable tools (PRISMA/MOOSE and AMSTRA-2). Furthermore, we quantified the number and impact of all changes that occurred in each non-Cochrane systematic review. Our results therefore represent a precise estimate of the prevalence of differences in the methods between non-Cochrane systematic reviews and their protocols.

Certain limitations of our study must be acknowledged. First, we only included the systematic reviews registered the protocol on PROSPERO within one year and published the full text, it is therefore impossible to observe whether the difference between the protocol and the full text has changed with the promotion of PRISMA-Protocol. Second, due to limited resources, we did not verify these changes and their reasons with each individual author. We only based on the reporting of the systematic reviews and their protocols, and therefore, the judgment of changes was also affected by the quality of the reporting, leaving the possibility that the changes did not reflect “the truth” as experienced by the authors themselves. 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, though we did not consider these published protocols.

Implications for future research

Future research should focus on the relationship between the reporting quality of the review protocol registered on PROSPERO and any differences with the actual study. The registry entry itself provides readers with a reference to compare against complete reviews, in the absence of an available protocol, to examine for reporting biases[59]. Thus, the quality of the reporting will affect the judgment of the differences between the protocol and the full text, and therefore affect the transparency of the systematic reviews. Currently, the reporting quality of PROSPERO's protocol may be poor without peer review and quality assessment, and our study supports this hypothesis. In addition, it is necessary to verify these changes as well as the explanations for these changes with the author in order to have a more comprehensive understanding behind the reasons for the changes and their impacts on the quality of the systematic reviews. It is also interesting to observe whether there are differences between the latest version of the protocol published in the peer-reviewed journal and recorded in PROSPERO, and whether there are differences between the two versions and the full text of the systematic reviews.

Conclusions

Differences between the non-Cochrane systematic reviews and their protocols recorded in PROSPERO are widespread, and there have been many changes that do not yet have a clear impact on the systematic reviews. Measures should be taken to further improve the transparency of the non-Cochrane systematic reviews. Guiding the author to report and explain the differences between the protocol and systematic reviews by adding these explanations in PRISMA and MOOSE or even requiring authors to so at the level of journal are two fundamental solutions that we offer.

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; AMSTRA-2:a critical appraisal tool for systematic reviews that include randomized or non-randomized studies of healthcare interventions, or both; ICJE:International Medical Journal Editors' Committee.

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; KY provided methodological support/advice; KH, ZS and YJ tested the feasibility of the study; KH, TZ, and WZ extract data; KH and QZ identify the categories and impact of change. YM, AW, GT, and JK performed the statistical analysis; KH 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.

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Figures

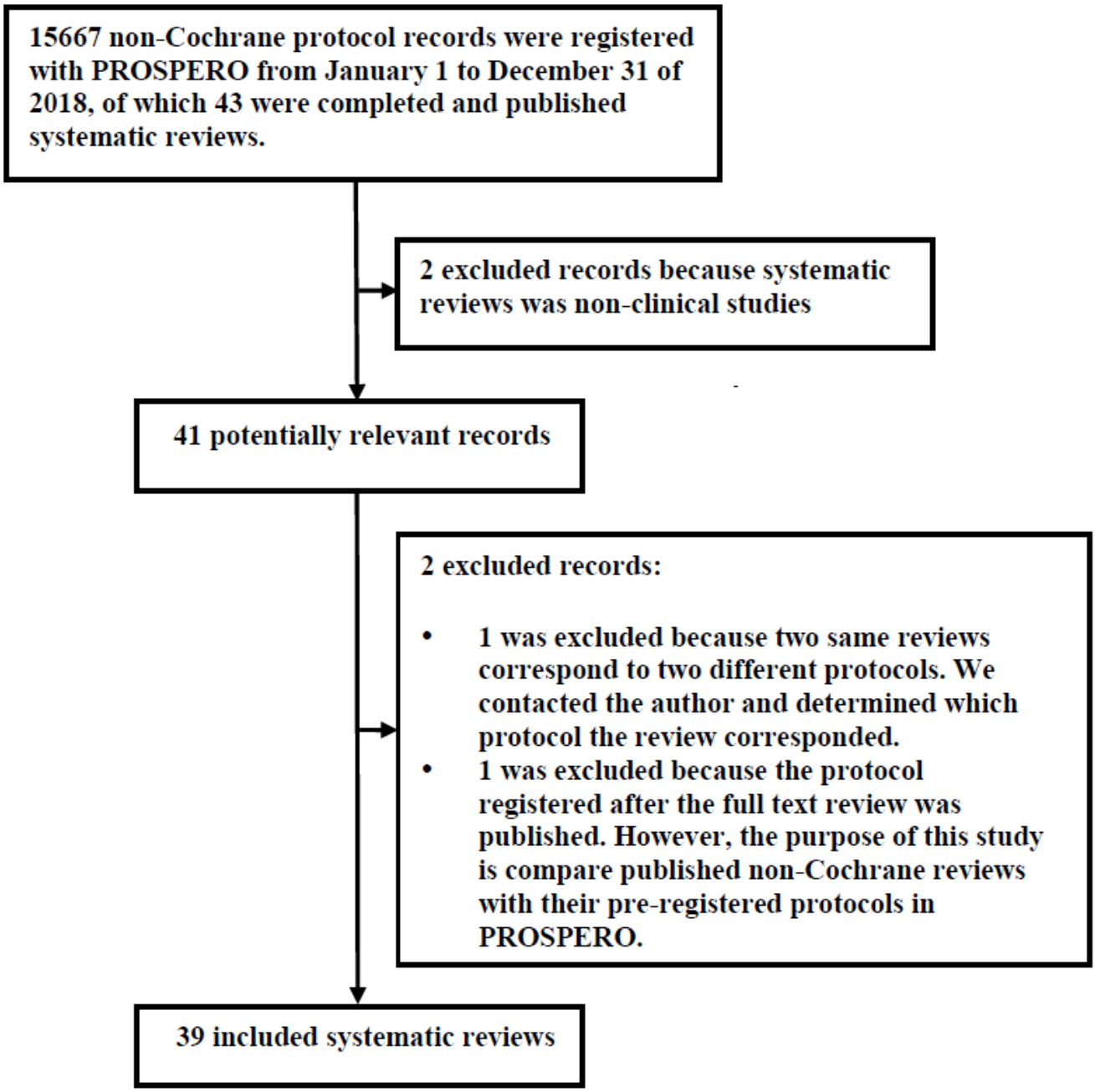

Figure 1

Flow diagram for the identification and selection of eligible systematic reviews in this study.

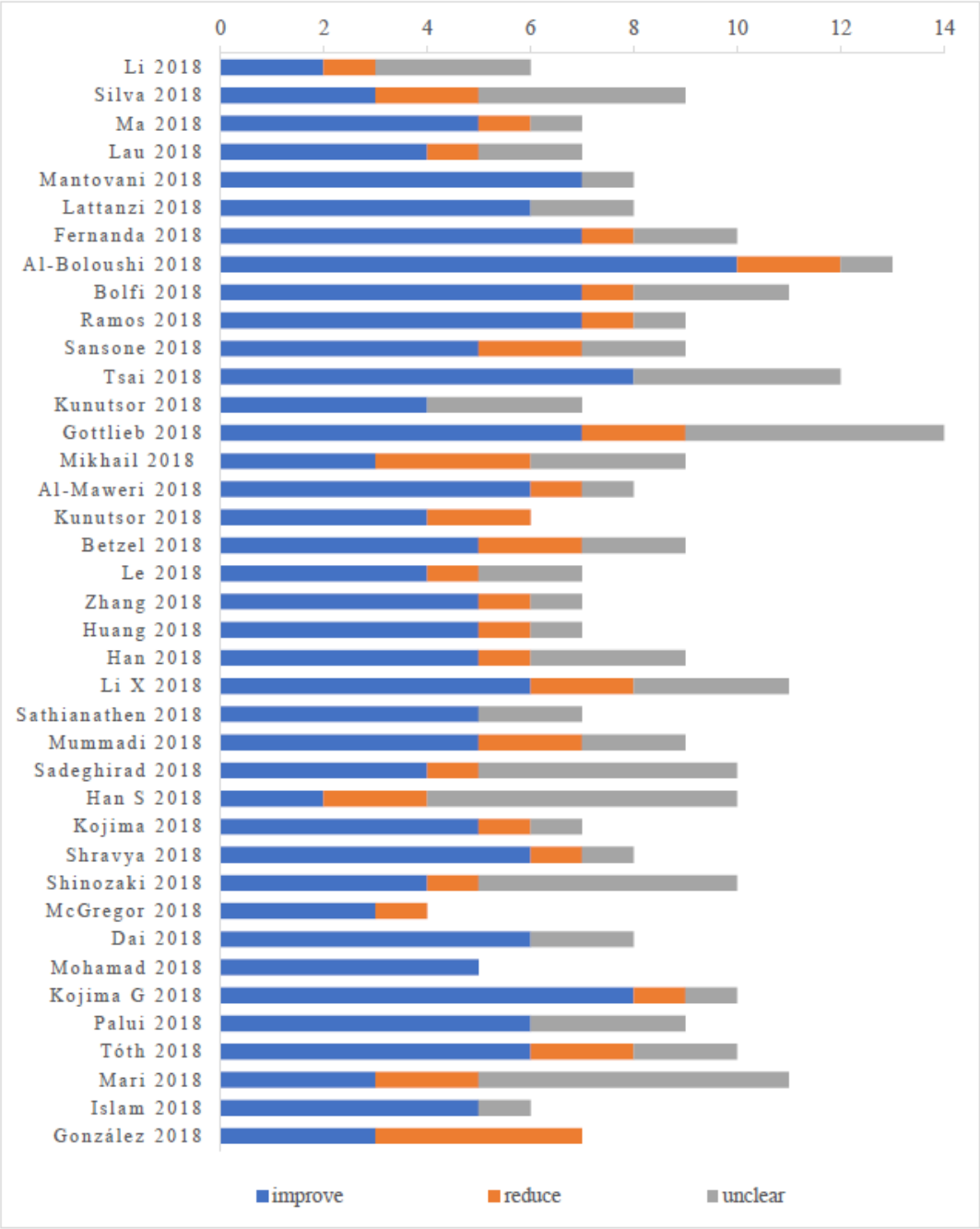

Figure 2

The number of systematic reviews that improved the quality, reduced the quality, or had an unclear impact for each compared methodology-related section.

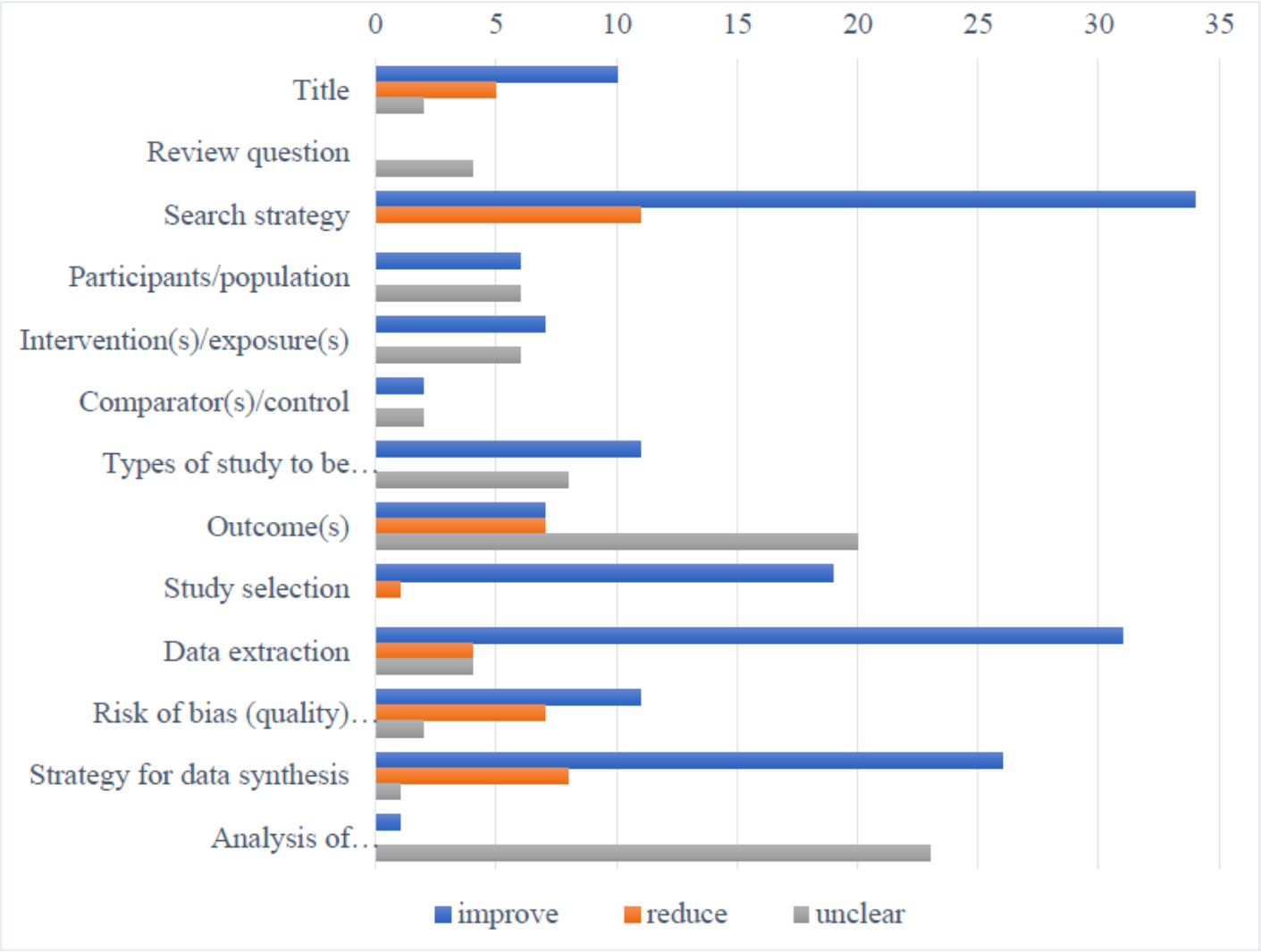

Figure 3

The distribution of changes that improve the quality, reduce the quality or have an unclear impact in each review.

Supplementary Files

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