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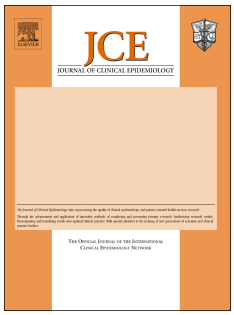

Association between prospective registration and overall reporting and methodological quality of systematic reviews: a meta-epidemiological study

Long Ge, PhD, Jin-hui Tian, PhD, Ya-nan Li, MPH, Jia-xue Pan, MPH, Ge Li, PhD, Dang Wei, MD, Xin Xing, MPH, Bei Pan, MD, Yao-long Chen, PhD, Fu-jian Song, PhD, Ke-hu Yang, MD

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Association between prospective registration and overall reporting and methodological quality of systematic reviews: a meta-epidemiological study

Long Ge[1,2,3#], PhD; Jin-hui Tian[2,3#], PhD; Ya-nan Li[2,3,4], MPH; Jia-xue Pan[4], MPH; Ge Li[5], PhD; Dang Wei[2,3], MD; Xin Xing[2,3,4], MPH; Bei Pan[4], MD; Yao-long Chen[2,3], PhD; Fu-jian Song[6*], PhD; Ke-hu Yang[2,3*], MD

1 The First Clinical Medical College of Lanzhou University, Lanzhou 730000, China
2 Evidence-Based Medicine Center, School of Basic Medical Sciences of Lanzhou University, Lanzhou 730000, China
3 Key Laboratory of Evidence-Based Medicine and Knowledge Translation of Gansu Province, Lanzhou 730000, China
4 School of Public Health, Lanzhou University, Lanzhou 730000, China
5 School of Chinese Medicine, Tianjin University of Traditional Chinese Medicine, Tianjin 300193, China
6 Norwich Medical School, Faculty of Medicine and Health Science, University of East Anglia, Norwich, Norfolk, UK

 # Ge L and Tian JH are co-first authors
***Co-Corresponding Author**
Ke-hu Yang, Evidence-based Medicine Center of Lanzhou University; Key Laboratory of Evidence-based Medicine and Knowledge Translation of Gansu Province, Lanzhou City, Gansu province, China. Email: kehuyangebm2006@126.com

Fu-jian Song, Norwich Medical School, University of East Anglia, Norwich, NR4 7TJ, U.K. Email: Fujian.Song@uea.ac.uk

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ABSTRACT

Objective: To investigate the differences in main characteristics, reporting and methodological quality between prospectively registered and non-registered systematic reviews.

Methods: PubMed was searched to identify systematic reviews of randomized controlled trials published in 2015 in English. After title and abstract screening, potentially relevant reviews were divided into three groups: registered non-Cochrane reviews, Cochrane reviews, and non-registered reviews. For each group, random number tables were generated in Microsoft Excel, and the first 50 eligible studies from each group were randomly selected. Data of interest from systematic reviews were extracted. Regression analyses were conducted to explore the association between total R-AMSTAR or PRISMA scores and the selected characteristics of systematic reviews.

Results: The conducting and reporting of literature search in registered reviews were superior to non-registered reviews. Differences in nine of the 11 R-AMSTAR items were statistically significant between registered and non-registered reviews. The total R-AMSTAR score of registered reviews was higher than non-registered reviews (MD=4.82, 95%CI: 3.70, 5.94). Sensitivity analysis by excluding the registration related item presented similar result (MD=4.34, 95%CI: 3.28, 5.40). Total PRISMA scores of registered reviews were significantly higher than non-registered reviews (all reviews: MD=1.47, 95%CI: 0.64-2.30; non-Cochrane reviews: MD=1.49, 95%CI: 0.56-2.42). However, the difference in the total PRISMA score was no longer statistically significant after excluding the item related to registration (item 5). Regression analyses showed similar results.

Conclusions: Prospective registration may at least indirectly improve the overall methodological quality of systematic reviews, although its impact on the overall reporting quality was not significant.

Keywords: Prospective registration; Quality; Systematic reviews; Meta-epidemiological study

What is new?

- **Key finding:** Prospective registration could indirectly improve the overall methodological quality of systematic reviews.
- **What this adds to what is known:** We conducted firstly a meta-epidemiological study to investigate the impact of prospective registration on reporting and methodological quality of systematic reviews. It was significantly meaningful that prospectively registered systematic reviews showed higher methodological quality than non-registered systematic reviews.
- **What is the implication, what should change now:** Many of published systematic reviews were poorly conducted and reported. Strategies improving the quality of systematic reviews should be explored to reduce this avoidable waste in research. A protocol written in advance of a systematic review may reduce bias in the conduct and reporting process, and should be performed in further training of authors of systematic reviews.

INTRODUCTION

Well-conducted systematic reviews and meta-analyses of randomized controlled trials are accepted as the best-quality evidence to inform policy and practice [1,2]. It was estimated that more than 8,000 systematic reviews were indexed in MEDLINE annually, corresponding to a 3-fold increase over the last decade [3]. However, many of published systematic reviews were poorly conducted and reported [3], and need to be improved in terms of the reporting and methodological quality.

A key feature of a high-quality systematic review is to pre-specify the main objectives, literature search strategy, inclusion/exclusion criteria, methods for data extraction and quality assessment, and planned analyses for the review in a protocol [4]. A protocol written in advance of a systematic review may reduce bias in the conduct and reporting process [4]. In order to enhance the transparency of review objectives and methods and avoid outcome reporting bias, the Cochrane Collaboration requests that a protocol should be prepared before conducting the Cochrane systematic review [5]. International Journal of Obstetrics and Gynaecology was the first journal to set up a system for the formal registration of protocols for systematic reviews of test accuracy studies in 2005 [6]. With the increasing momentum of support for prospective registration of protocols for systematic reviews, an International Prospective Register of Systematic Reviews (PROSPERO) was established in 2011 and is the only open-access online facility to prospectively register non-Cochrane systematic reviews [7]. After that, many organisations and networks (e.g., NIHR, WHO, Cochrane and Campbell Collaborations), and publishers (e.g., PLoS journals, BMJ, BioMed Central) have expressed their support for the prospective registration of systematic review protocols [7]. Currently, there are over 15,000 systematic reviews registered on PROSPERO, and more than 1,500 records are marked as completed or published. However, there is a lack of empirical evidence about whether prospective registration of protocols improves the overall reporting and methodological quality of systematic reviews. According to our knowledge, there are no previous published studies that systematically compared quality of non-Cochrane systematic reviews of healthcare interventions that were prospective registered and those that were not registered.

The primary objective of this study was to investigate differences in the main characteristics, reporting and methodological quality between registered (including Cochrane reviews) and non-registered systematic reviews. Secondary objectives were to compare the differences between registered non-Cochrane systematic reviews and non-registered systematic reviews, and explore the association between overall reporting and methodological quality and selected characteristics of systematic reviews.

METHODS

Eligibility criteria

We included systematic reviews with or without meta-analysis that met the following criteria: (1) explicitly stated methods to identify studies, explicitly stated methods of study selection, and explicitly described the methods of evidence synthesis; (2) were fully published in English language in 2015, and (3) included only randomised controlled trials (RCTs) to evaluate clinical effects of healthcare interventions.

We excluded systematic reviews that included both RCTs and non-randomised studies, didn't focus on healthcare interventions (e.g., diagnostic, etiology, and prognosis), methodology reviews, scoping or

rapid reviews, umbrella overviews, review protocols, abstracts/proceedings, and letters to editors.

Identification and selection of systematic reviews

PubMed was searched on June 11th 2016 to identify relevant systematic reviews and meta-analyses. The search strategy was "(randomised[Title/Abstract] OR randomized[Title/Abstract] OR RCTs[Title/Abstract]) AND (Meta-Analysis[ptyp] OR systematic[sb])". The search date was limited from 1st January 2015 to 31st December 2015. The search strategy was developed by one reviewer (LG), with support from two senior reviewers (J-HT and K-HY) who both have more than 10 years' experience as information specialists.

Literature search records were imported into ENDNOTE X6 literature management software. Two independent reviewers (LG, JL) examined the title and abstract of retrieved records to identify possibly relevant reviews, and independently examined full-text of potentially relevant reviews according to the eligibility criteria. Conflicts were resolved by a third reviewer (J-HT, or K-HY).

Study design

This is a comparative meta-epidemiological study to investigate whether prospective registration is associated with methodological and reporting quality of systematic reviews. Registration status of non-Cochrane systematic reviews was initially decided according to whether the registration information was provided in abstract, or whether a protocol was mentioned in abstract. After title and abstract selection, potentially relevant reviews were divided into three groups: registered non-Cochrane systematic reviews, Cochrane systematic reviews, and non-registered systematic reviews. Registered systematic reviews were those that had a protocol in advanced of the review no matter whether a registration number was available or not. Because the number of registered non-Cochrane systematic reviews is predictably small for one year, registered systematic reviews consist of registered non-Cochrane systematic reviews and Cochrane reviews. For each group, the random number tables were generated in Microsoft Excel (Microsoft Corp, Redmond, WA, www.microsoft.com), and the first 50 eligible studies from each group were selected. If a selected systematic review was not eligible after reading the full-text, a successive record was used to replace it until the total number of included systematic reviews was 50 for each of the three groups. Random selection of systematic reviews was carried out by one reviewer (LG).

Data extraction and management

A draft data extraction form was developed using Microsoft Excel 2013 (Microsoft Corp, Redmond, WA, www.microsoft.com). Reviewers involved in data extraction piloted the form on a random sample of five included systematic reviews to ensure consistency in interpretation of data items. The form was revised when considered necessary. Then, one of three reviewers (LG, Y-NL, or J-XP) extracted data from the included systematic reviews, and another reviewer (J-H T or K-H Y) checked the extracted data. Any conflicts were resolved by discussion.

Data of interest from systematic reviews included general review characteristics, reporting of literature search, methodological quality based on Revised Assessment of Multiple Systematic Reviews (R-AMSTAR) checklist [8], and reporting quality based on Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement [10].

General review characteristics

The following general review characteristics were collected: first author's name, year of publication,

country of the corresponding author, journal name, funding source, number of authors, number of included randomised controlled trials, total number of patients included, original or updated systematic reviews, protocol register, categories of disease, and type of interventions. The details of items extracted are presented in Appendix 1.

Reporting of literature search methods

We obtained the following information on literature search methods: the number and name of electronic bibliographic databases searched, year of coverage, search terms reported, the search strategy provided, the number and name of other sources searched (e.g., reference lists checking, clinical trial registration platform, conference abstracts or web sites, Google engine).

Methodological quality assessment

We assessed the methodological quality of included systematic reviews using the R-AMSTAR checklist [8], which was the revised version of the AMSTAR [9]. Compared to the original AMSTAR, the R-AMSTAR could be used more conveniently to quantify the methodological quality of published systematic reviews [8]. Each of the R-AMSTAR checklist items can be scored from 1 to 4, according to whether the assessed criterion was explicitly met in the systematic review: The score is '1' if zero or one criteria was met, and '4' if all criteria were met. A greater R-AMSTAR score indicates the higher methodological quality of a systematic review. The detailed R-AMSTAR checklist and assessment criteria are shown in Appendix 2.

Reporting quality assessment

The reporting quality of included systematic reviews was assessed according to the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) [10], which is a checklist with twenty seven items. To indicate the degree of compliance, each checklist item was assigned one of the following four responses: 'Yes' for total compliance; 'Partial' for partial compliance; 'No' for noncompliance; and 'Cannot answer' for limited information. The total score of reporting quality was obtained by summing '1' point for each 'yes', '0.5' for each 'partial', and '0' point for any other responses ('No', and 'Cannot answer').

Data analysis

We compared the general review characteristics, reporting of literature search methods, and the methodological and reporting quality between registered (including Cochrane reviews) and non-registered systematic reviews, and between non-Cochrane registered systematic reviews and non-registered reviews. We used frequency and percentage for categorical variables (including data on individual items of R-AMSTAR and PRISMA), and median and interquartile range (IQR) for continuous variables. Chi-squared test was used to statistically test differences in categorical items, and nonparametric statistical approach (two sample Wilcoxon rank-sum test) or student t test to test differences in continuous items. Fisher's exact test was used if a contingency table contained a cell with 5 or fewer events.

For each of the 27 PRISMA items, we summarized the frequency of 'Yes' response to all included systematic reviews, and calculated odds ratio (OR) with 95% confident intervals (95% CI) to compare the compliance between registered and non-registered systematic reviews. The OR value represents the relative frequency of 'Yes' responses in group one versus that in group two. For each item, OR>1 indicates that the odds of compliance in the group one is greater than in the group two. For each of the 11 R-AMSTAR item, we calculated mean score and standard deviation (SD). The mean difference (MD)

and 95% CI were calculated for each item to compare the overall methodological quality between comparison groups. The MD value represents the difference in the mean score between group one and group two. MD>0 indicates that the group one had a mean score higher than the group two.

Either bivariate or multiple variable linear regression analyses were conducted to explore the association between total R-AMSTAR scores or PRISMA scores (as the dependent variable) and the selected characteristics of systematic reviews. Relevant analyses were conducted by using data from all included systematic reviews and by excluding Cochrane reviews. Statistical significance was defined as two sided $P \leq 0.05$.

In addition, we performed sensitivity analyses to inspect the robustness of results by excluding the item related to registration (item 1 for R-AMSTAR, item 5 for PRISMA). We used JMP version 13.0 for statistical analyses.

RESULTS

Search results

Initial literature search retrieved 8,131 citations. Based on titles and abstracts, 3,044 citations were excluded. Of them, 854 were published in 2016, 1,052 were not systematic reviews, and 1,138 included non-randomized studies. 5,087 citations were divided into three groups, and 50 samples were randomly selected for each group (Figure 1). The citations of included systematic reviews can be found in Appendix 3.

General characteristics of included systematic reviews

The general characteristics of the included reviews are shown in Table 1. The included systematic reviews were conducted in 28 different countries, mostly in the UK (22.0%), China (19.3%), the USA (12.0%), and Australia (9.3%) (Figure 2). The included systematic reviews were concerning a wide range of disease categories, including diseases of the musculoskeletal system and connective tissue (11.3%), mental and behavioral disorders (10.7%), and diseases of the circulatory system (10.0%) (Figure 3).

The registered non-Cochrane reviews were registered in PROSPERO (88%), and/or published the review protocols in peer-reviewed journals (16%). Of the registered non-Cochrane systematic reviews, 58% were published in specialty journals. Most (94%) were indexed in Science Citation Index (SCI) database, and the median impact factor was 3.057 (IQR: 2.562-5.722). These reviews included a median of 11 RCTs and a median number of 1,549 patients. 56% of the registered non-Cochrane reviews reported the sources of funding, 96% were sponsored by non-profile organizations, and 72% investigated a non-pharmacological intervention. The Cochrane reviews included a median of 8 RCTs involving 1,265 patients. 82% of the Cochrane reviews were sponsored by non-profile organizations, and 64% investigated a non-pharmacological intervention. Compared with the registered reviews, the non-registered systematic reviews were less likely to be indexed in SCI (88% vs.97%, P=0.04), with a lower median impact factor (2.448 vs. 6.103, P<0.001), and less likely with funding from non-profit sponsor (26% vs. 69%, P<0.001).

Reporting of literature search methods

All included reviews provided information on literature search (Appendix 4). The median number of electronic bibliographic databases searched in the registered reviews was greater than in the non-registered reviews (5 vs. 4, P<0.001). The year of coverage was reported in 64% of the registered

reviews, compared to 44% of the non-registered reviews (P=0.02). More registered reviews reported full search strategies compared with the non-registered reviews (82% vs. 34%, P<0.001). PubMed/MEDLINE (95% vs. 98%, P=0.53), EMBASE (87% vs. 66%, P=0.003), and CENTRAL (51% vs. 18%, P<0.001) were the common databases searched. Compared to non-registered reviews, more registered reviews searched clinical trial registries (P=0.03), reference lists (P=0.03), ongoing trials (P<0.001) and abstracts/proceeding (P=0.003).

Methodological quality of included systematic reviews

The R-AMSTAR checklist consists of 11 items involving 50 assessment points, and details of R-AMSTAR scores are shown in Appendix 5. Responses to 58% of the assessment points were statistically significant between registered and non-registered reviews. For 9 of the 11 R-AMSTAR items, the differences in the score were statistically significant between registered and non-registered systematic reviews (Figure 4, Appendix 6-8). The total R-AMSTAR score of the registered reviews was higher than the non-registered reviews (MD=4.82, 95%CI: 3.70, 5.94). Sensitivity analysis by excluding item related to registration presented similar result (MD=4.34, 95%CI: 3.28, 5.40) (Appendix 6). After excluding Cochrane reviews, 5 of the 11 R-AMSTAR items had significant differences between the registered non-Cochrane reviews and non-registered reviews. In sensitivity analysis, total R-AMSTAR scores of the registered non-Cochrane reviews remained higher than the non-registered reviews (Appendix 7). However, these scores were relatively low compared with Cochrane reviews (total scores: MD=-3.92, 95%CI: -4.94, -2.90; sensitivity analysis: MD=-3.44, 95%CI: -4.42, -2.46) (Appendix 8).

Reporting quality of included systematic reviews

Figure 5 shows reporting quality of systematic reviews, measured with total compliance for each of the 27 PRISMA items. Except for item related to registration (item 5), the total compliance rates of item 2, item 4, item 8, item 18, and item 27 were significantly higher in the registered reviews than in the non-registered reviews (Figure 5, Appendix 9). After excluding Cochrane reviews, differences in item 4 and item 18 were no longer statistically significant, while differences in item 16 and item 23 became statistically significant (Figure 5, Appendix 10). When compared to Cochrane reviews, the total compliance rates of 6 items were significantly lower in the registered non-Cochrane reviews (Figure 5, Appendix 11). Figure 6 shows that the total PRISMA scores of the registered reviews (no matter whether Cochrane reviews were included) were significantly higher than the non-registered reviews. However, there were no statistically significant differences between them when item related to registration (item 5) was excluded.

Results of regression analyses

Using data from all systematic reviews, the total R-AMSTAR scores were statistically significantly associated with registration status, impact factors, and funding sources in either bivariate or multiple variable linear regression analyses (Appendix 12-1). The differences in sensitivity analyses and analyses after excluding Cochrane reviews remained significant (Appendix 12-1, 2). Total PRISMA scores were significantly associated with registration status and funding sources when all systematic reviews were included in either bivariate or multiple variable linear regression analyses (Appendix 12-3). After excluding Cochrane reviews, the differences remained significant (Appendix 12-4). However, the differences of registration status were no longer significant in sensitivity analyses (Appendix 12-3, 4).

DISCUSSION

Summary of finding

Currently, most of methodological studies focused on the transparency and selective reporting bias of outcomes of systematic reviews [11-13]. A registry of protocols of systematic reviews might reduce publication bias, enhance transparency and avoid duplication of effort [14]. Present study firstly focused on the association between prospective registration and overall reporting and methodological quality of systematic reviews. Results indicated that prospective registration could improve the overall methodological quality of systematic reviews, but only slightly improved overall reporting quality. Sensitivity analyses, analyses after excluding Cochrane reviews, and regression analyses showed similar results.

Compared with non-registered reviews, registered reviews (either Cochrane or non-Cochrane reviews) were more likely to be published in SCI journals with higher impact factors and to be financially sponsored. Most of the included registered non-Cochrane reviews were registered in PROSPERO, which was the only open-access online facility to prospectively register non-Cochrane systematic reviews. Some peer-reviewed journals, like *BMJ Open* and *Systematic Review*, are publishing protocols of planned or ongoing systematic reviews. However, only 16% registered non-Cochrane reviews published corresponding protocols in peer-reviewed journals. What's more, there were no statistical differences in interventions concerned between registered and non-registered reviews. For literature search reporting, the conduct and reporting of registered reviews were superior to non-registered reviews. Compared to non-registered reviews, registered reviews searched more electronic bibliographic databases, and search terms, search strategies, and clinical trial registers searched were more comprehensive. Furthermore, it was more common for registered reviews to search EMBASE, CENTRAL, CINAHL, and LILACS. An additional phenomenon was that Chinese databases were searched rarely in all included systematic reviews. To our knowledge, there were no relevant studies to investigate the impact of Chinese clinical trials inclusion on estimates of intervention effects and diagnostic accuracy in performing systematic reviews. However, previous study indicated that Chinese biomedical databases should be searched when performing systematic reviews [15]. Actually, Cochrane Handbook also recommended the search of at least one Chinese databases like Chinese biomedical literature database [5], although this recommendation has not been widely implemented in Cochrane reviewers [15].

For methodological quality based on R-AMSTAR scores, registered reviews (including Cochrane reviews or not) were superior to non-registered reviews, especially regarding to the duplication of study selection and data extraction, rigor of literature search, consideration of publication status, and reporting of conflict of interest. Our study focused on the association between registration and reporting and methodological quality of systematic reviews, therefore, we performed sensitivity analyses by excluding item related to registration. Results were not materially different before and after excluding the registration-related item from the R-AMSTAR items. For reporting quality, there were no statistical differences in most of the PRISMA items between registered and non-registered reviews. The total PRISMA score of registered reviews was higher than non-registered reviews, although the difference was no longer statistically significant after excluding item 5 (protocol and registration) or Cochrane reviews. The direct comparison of methodological and reporting quality scores in systematic reviews from different groups may be confounded by certain review characteristics. Therefore, we conducted bivariate or multiple variable linear regression analyses to adjust for multiple review

characteristics. The overall differences in methodological quality between registered and non-registered systematic reviews remained statistically significant after adjusting for multiple review characteristics.

Exploring strategies improving the quality of systematic reviews

Reporting and methodological quality of published systematic reviews have been examined in numerous previous studies. A search of PubMed on October 10th 2016, using a high specificity search strategy ((("systematic review*"[Title] OR "meta analys*"[Title])) AND (((quality[Title] OR compliance[Title] OR methodological[Title] OR reporting[Title])) [16], identified 1,780 studies on the assessment of quality of systematic reviews. Consistency with a recent study published in *PLoS Medicine* [3], previous studies usually indicated that the reporting and methodological quality of published systematic reviews needed to be further improved with respect to some quality items. Strategies improving the quality of systematic reviews should be explored to reduce this avoidable waste in research. The subgroup analyses of our previous study focused on systematic reviews of diagnostic tests published by Chinese authors showed that compliance rates of some PRISMA items were improved for systematic reviews sponsored with funding [17]. Another study focused on systematic reviews published in "evidence-based" Chinese journals showed that factors associated with higher reporting quality of systematic reviews included papers with funding and papers conducted collaboratively by hospital staff and university researchers [18].

Present study focused on the impact of prospective registration on overall reporting and methodological quality of systematic reviews, especially regarding to study selection, data extraction, literature search, consideration of publication status, and reporting of conflict of interest. Results indicated that systematic reviews registered in advance showed higher methodological quality. However, prospective registration in itself would not improve the quality of systematic reviews. We had to consider more direct factors such as researchers' conceptual knowledge on systematic reviews. Researchers of registered systematic reviews might master more skills in conducting high quality systematic reviews. Prospectively registration of systematic reviews requires the development of a review protocol, and researchers to be more familiar with the requirements by PRISMA and PROSPERO. Therefore, prospective registration may be at least an indirect strategy to improve the methodological quality of systematic reviews.

Strengths and limitations

Prospective registration of protocols in advance was a key feature of a high-quality systematic review [4]. The present study is the first meta-epidemiological study to investigate the impact of prospective registration on reporting and methodological quality of systematic reviews. It was significantly meaningful to find that prospective registration improves the methodological quality of systematic reviews. Cochrane reviews have higher reporting and methodological quality than systematic reviews published in journals [3,19]. Therefore, we compared the differences of general characteristics, literature search, reporting and methodological quality before and after excluding Cochrane reviews. Because we are concerned about the impact of registration, we performed sensitivity analyses by excluding registration or protocol related items from the R-AMSTAR and PRISMA checklist.

There were some limitations in our study. Firstly, registration status of non-Cochrane systematic reviews was initially decided according to whether the registration information was reported in abstract, or whether a protocol was mentioned in abstract. There were non-Cochrane systematic reviews prospectively registered, but did not mention the protocol or registration in abstract. This may introduce

selection bias in the process of identifying registered systematic reviews, although the impact of such potential bias is unlikely to be considerable. Secondly, we searched only PubMed database with high-specificity search terms to identify systematic reviews published in 2015. However, there are no reasons to suspect that the results will be much different if more databases were searched to identify published systematic reviews. In addition, we included only systematic reviews of RCTs published in English, the finding may not be generalizable to systematic reviews of other types (e.g., observational studies, diagnostic tests) and systematic reviews published in other languages. Because we only included systematic reviews published in 2015, it was not possible to observe the association of prospective registration and quality over time. Thirdly, there were still some argument for methodological quality assessment tools of systematic review. Previous study found original AMSTAR had better measurement properties than R-AMSTAR [20]. However, original AMSTAR items also have some drawbacks [21]. The R-AMSTAR overcome some drawbacks of the original AMSTAR and could more conveniently quantify the quality of systematic reviews. Fourthly, the assessment of methodological quality of systematic reviews was based on what was reported by authors, and the actual conduct might be different. Fifthly, we included funding sources as an independent variable in regression analyses, and results showed that the total R-AMSTAR scores and PRISMA scores were statistically significantly associated with funding sources in either bivariate or multiple variable linear regression analyses. However, funding source was the variable that contributed to quality scores. Finally, we were mainly concerned about the registration status of systematic reviews in this study, and further studies are needed to explore other strategies for improving the quality of systematic reviews, such as the impact of funding sources.

In conclusions, prospective registration could be a strategy to improve the overall methodological quality of systematic reviews, although its impact on the overall reporting quality was not significant. Further studies are required to investigate causes of the observed association of prospective registration of protocols and the methodological quality of published systematic reviews.

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Authors' contributions: GL, TJH, and YKH planned and designed the research; SFJ, and CYL provided methodological support/advice and polish the manuscript; GL and WD tested the feasibility of the study; GL, PB, LYN, PJX, and XX extract data; GL and LG performed the statistical analysis; GL wrote the manuscript; all authors approved the final version of the manuscript.

Conflicts of Interest: None

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SUPPLEMENTARY MATERIAL

Appendix 1 - Data extraction: basic information and reporting of literature search

Appendix 2 - Revised AMSTAR checklist

Appendix 3 - Citations of included systematic reviews

Appendix 4 - Reporting of literature search methods
Appendix 5 - Details of R-AMSTAR assessment
Appendix 6 - R-AMSTAR scores of registered vs non-registered
Appendix 7 - R-AMSTAR scores of registered non-CC vs non-registered
Appendix 8 - R-AMSTAR scores of registered non-CC vs CC
Appendix 9 - PRISMA scores of registered vs non-registered
Appendix 10 - PRISMA scores of registered non-CC vs non-registered
Appendix 11 - PRISMA scores of registered non-CC vs CC
Appendix 12 Results of regression analyses
Appendix 12-1 Results of regression analyses for variables associated with R-AMSTAR scores (All systematic reviews)
Appendix 12-2 Results of regression analyses for variables associated with R-AMSTAR scores (Non-Cochrane systematic reviews)
Appendix 12-3 Results of regression analyses for variables associated with PRISMA scores (All systematic reviews)
Appendix 12-4 Results of regression analyses for variables associated with PRISMA scores (Non-Cochrane systematic reviews)

Figure legends

Figure 1. The flow diagram of literature selection
Figure 2. Countries of included systematic reviews (Ordered by number of registered non-Cochrane reviews)
Figure 3. Categories of disease of included systematic reviews (Ordered by number of registered non-Cochrane reviews)
Figure 4. Results of R-AMSTAR score
Figure 5. Results of PRISMA assessment
Figure 6. Results of total PRISMA score

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Table 1 The characteristics of systematic review included systematic reviews

Characteristics	Registered (n=100)		Non-registered (n=50)	P value (Registered vs. non-registered)
	Non-Cochrane (n=50)	Cochrane (n=50)		
Category of journals: %				
- General	29 (58.0)	0 (0.0)	23 (46.0)	0.04
- Specialty	21 (42.0)	50 (100.0)	27 (54.0)	0.04
Indexed in SCI journals: %	47 (94.0)	50 (100.0)	44 (88.0)	0.04
Journal impact factor: median (IQR)	3.057 (2.562, 5.722)	6.103	2.448 (1.776, 3.489)	<0.001
No. of authors: median (IQR)	5 (4, 7.75)	4 (3,5.75)	5 (4, 7)	1.00
No. of RCTs included: median (IQR)	11 (7.75, 17.5)	8 (3.25, 20)	9 (5.57, 14.25)	0.73
No. of patients included: median (IQR)	1549 (801.25, 3567)	1265 (477, 3579)	956 (465.25, 2009.25)	0.07
Funding sources: %				
- Non-profit sponsor	27 (54.0)	41 (82.0)	13 (26.0)	<0.001
- For-profit sponsor	1 (2.0)	0 (0.0)	0 (0.0)	0.80
- None	14 (28.0)	2 (4.0)	11 (22.0)	0.37
- Unclear	3 (6.0)	0 (0.0)	8 (16.0)	0.01
- Not reported	5 (10.0)	7 (14.0)	18 (36.0)	<0.001
The name of the registers: %				
-PROSPERO	44 (88.0)	0 (0.0)	0 (0.0)	0.002
-Cochrane	0 (0.0)	50 (100.0)	0 (0.0)	0.001
-Others	6 (12.0)	0 (0.0)	0 (0.0)	0.19
Is published protocol available? (Yes) %	8 (16.0)	50 (100.0)	0 (0.0)	<0.001
Category of interventions: %				
- Pharmacological	10 (20.0)	18 (36.0)	7 (14.0)	0.06
- Non-pharmacological	36 (72.0)	32 (64.0)	37 (74.0)	0.45
- Both	4 (8.0)	0 (0.0)	6 (12.0)	0.08

Note: SCI, Science Citation Index; IQR, interquartile range; NA, not application

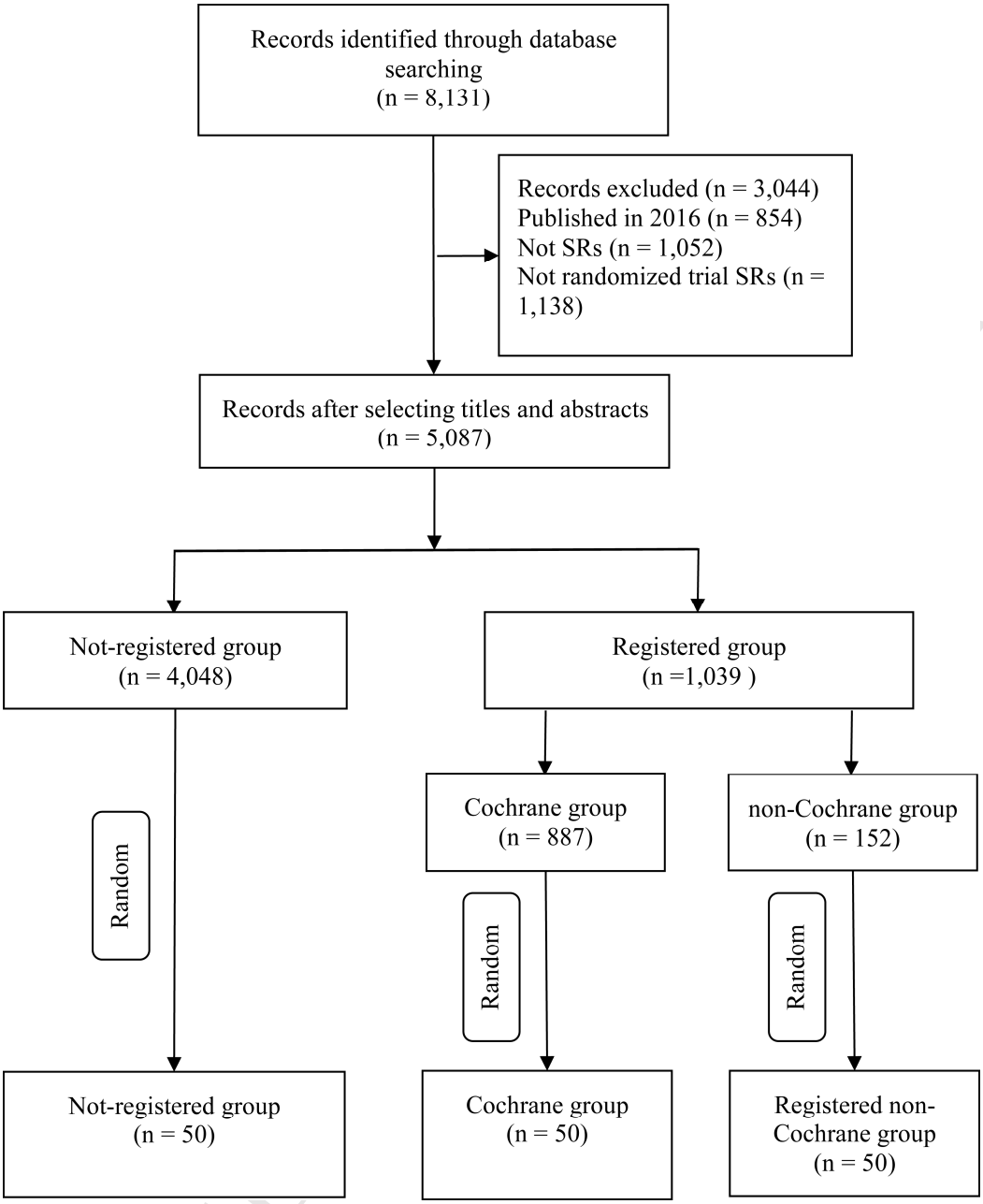

Figure 1.

The flow diagram of literature selection

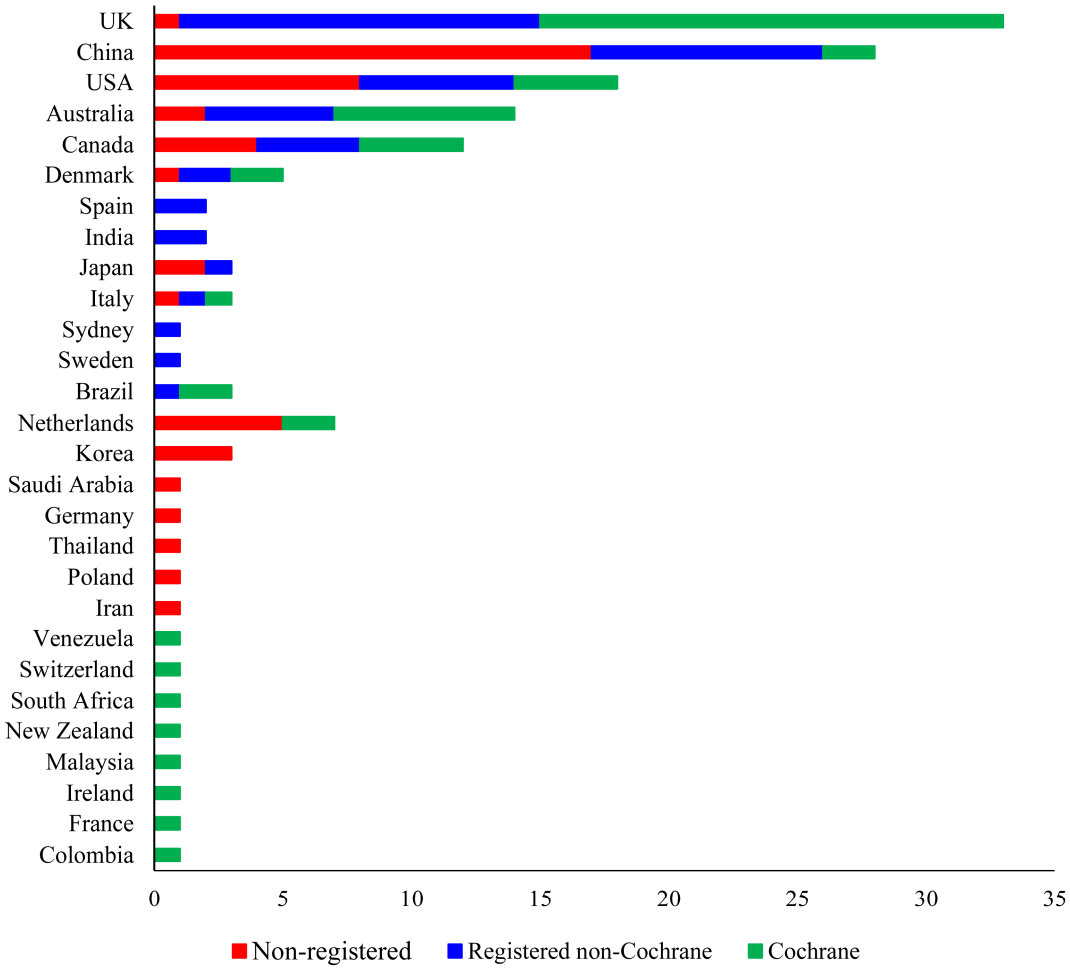

Figure 2.

Countries of included systematic reviews (Ordered by number of registered non-Cochrane reviews)

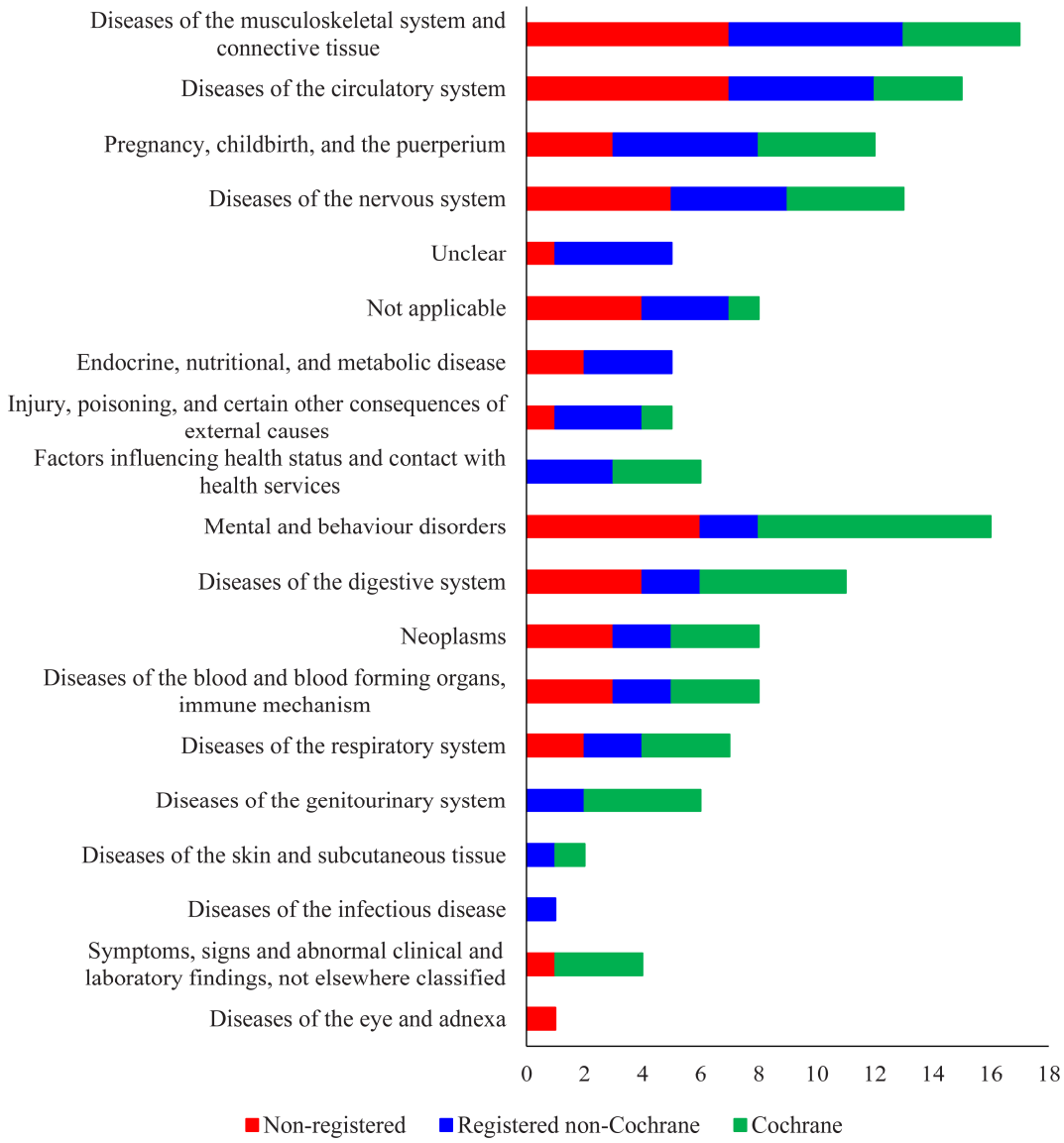

Figure 3.

Categories of disease of included systematic reviews (Ordered by number of registered non-Cochrane reviews): Unclear, indicates that included systematic reviews can't be classified according to ICD-10, such as adult critically ill patients; Not applicable, indicates that the topic of included systematic reviews doesn't focus on disease, such as responses to food price changes or adherence to drug treatment.

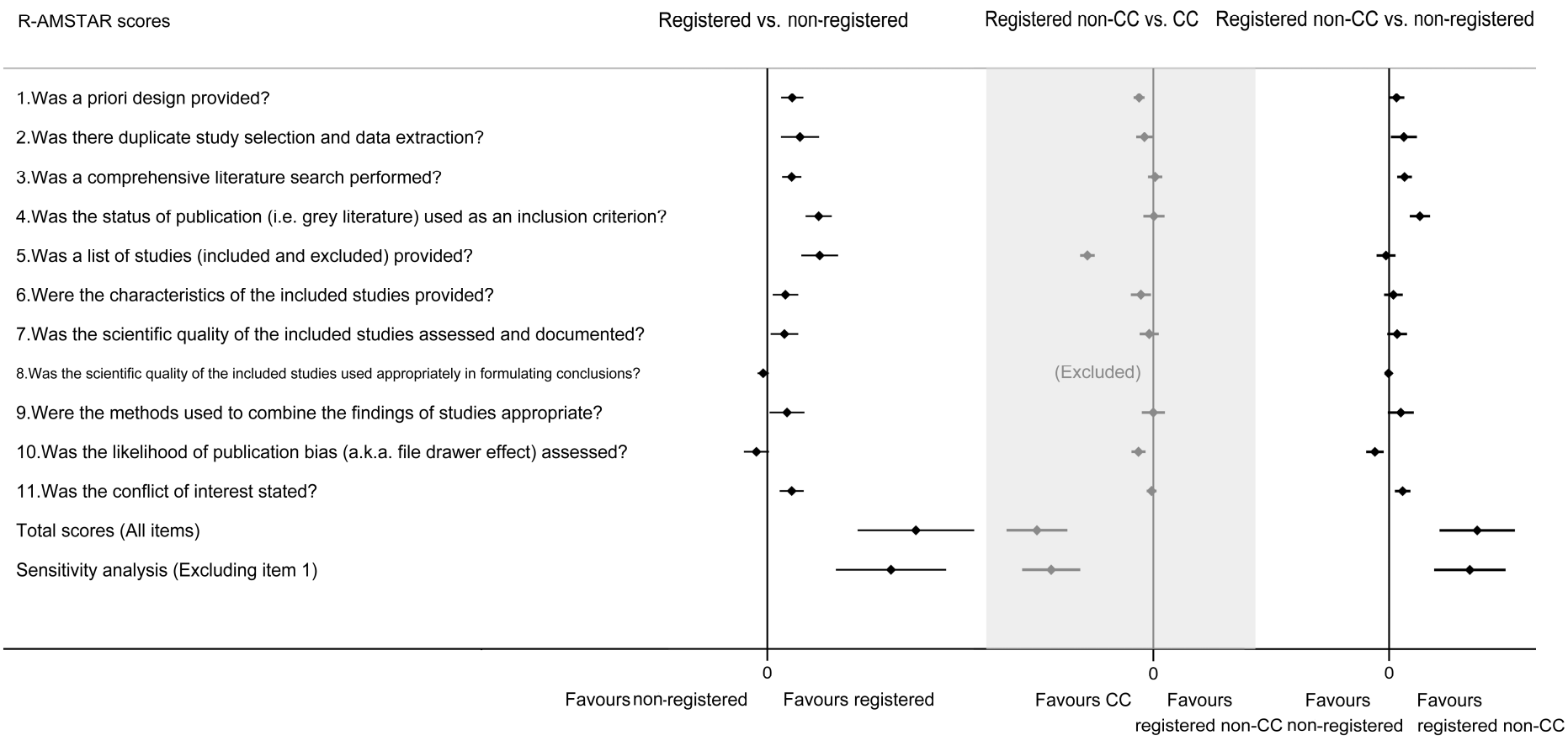

Figure 4.
Results of R-AMSTAR score

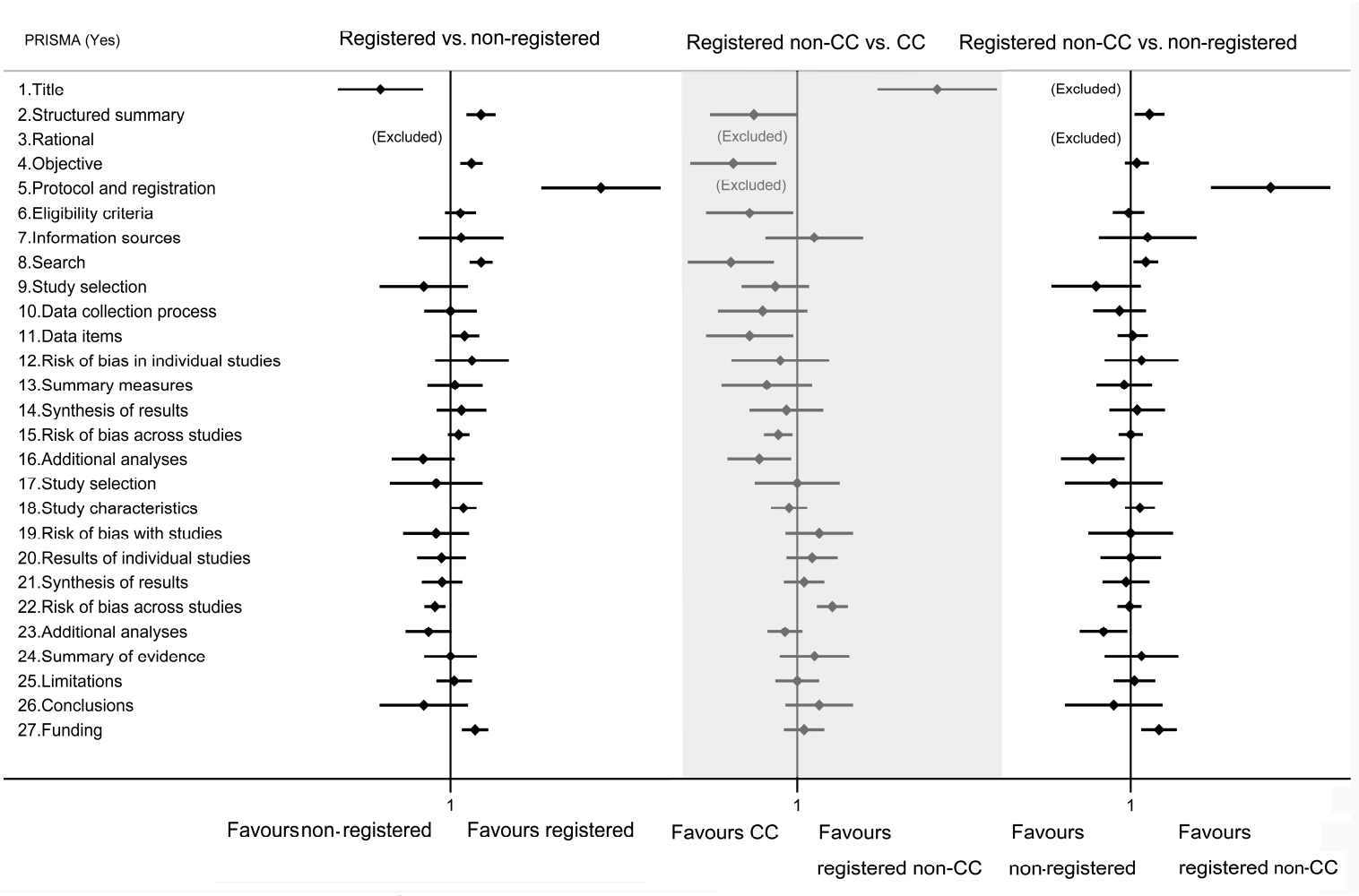

Figure 5.

Results of PRISMA assessment

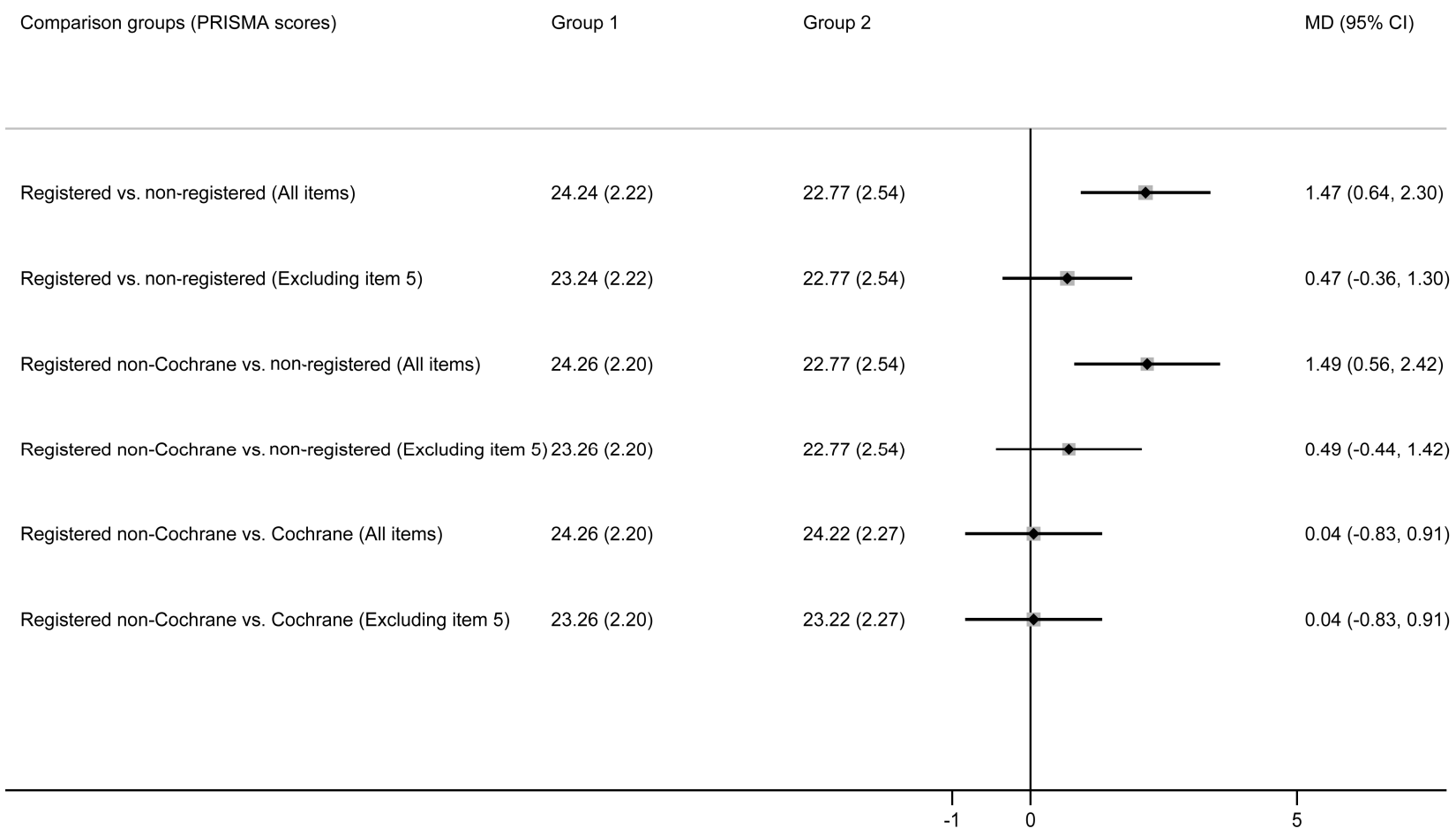

Figure 6.

Results of total PRISMA score

- **Highlights:**

- Key finding: Prospective registration may at least indirectly improve the overall methodological quality of systematic reviews.

- What this adds to what is known: We conducted firstly a meta-epidemiological study to investigate the impact of prospective registration on reporting and methodological quality of systematic reviews. It was significantly meaningful that prospective registration improved the methodological quality of systematic reviews.

- What is the implication, what should change now: Many of published systematic reviews were poorly conducted and reported. Strategies improving the quality of systematic reviews should be explored to reduce this avoidable waste in research. A protocol written in advance of a systematic review may reduce bias in the conduct and reporting process, and should be performed in further training of authors of systematic reviews.