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A Systematic Assessment of Cochrane Reviews and Systematic Reviews Published in High-Impact Medical Journals Related to Cancer

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Abstract

Objective: To compare cancer-related systematic reviews (SRs) published in the Cochrane Database of SRs (CDSR) and high-impact journals, with respect to type, content, quality, and citation rates.

Design: Methodological SR with assessment and comparison of SRs and meta-analyses. Two authors independently assessed methodological quality using an Assessment of Multiple Systematic Reviews (AMSTAR) –data based extraction form. Both authors independently screened search results, extracted content-relevant characteristics, and retrieved citation numbers of the included reviews using Clarivate Analytics Web of Science database.

Data sources: Cancer-related SRs were retrieved from the CDSR, as well as from the ten journals which publish oncologic SRs and had the highest impact factors, using a comprehensive search in the CDSR and MEDLINE.

Eligibility criteria for selecting studies: We included all cancer-related SRs and meta-analyses published from January 2011 to May 2016. Methodological SRs were excluded.

Results: We included 346 applicable Cochrane reviews and 215 SRs from high-impact journals. Cochrane reviews consistently met more individual AMSTAR criteria, notably with regards to an a-priori design (RR 3.89; 95% CI 3.10 to 4.88), inclusion of the grey literature and trial registries (RR 3.52; 95% CI 2.84 to 4.37) in their searches, and the reporting of excluded studies (RR 8.80; 95% CI 6.06 to 12.78). Cochrane reviews were less likely to address questions of prognosis (RR 0.04; 95% CI 0.02 to 0.09), use individual patient data (RR 0.03; 95% CI 0.01 to 0.09), or be based on non-randomised controlled trials (RR 0.04; 95% CI 0.02 to 0.09). Citation rates of Cochrane reviews were notably lower than those for high-

impact journals (Cochrane reviews: mean number of citations 6.52 (range 0 to 143); High-impact journal SRs: 74.45 (0 to 652)).

Conclusions: When comparing cancer-related SRs published in the CDSR versus those published in high-impact medical journals, Cochrane reviews were consistently of higher methodological quality, but were cited less frequently.

Strengths and limitations of this study

-Unique cross-disciplinary comparison of systematic reviews in oncology including over 550 SRs.

-Methodological assessment using AMSTAR, a validated and widely used tool to evaluate the quality of systematic reviews.

-It was not feasible to blind the authors of this study to the source journal of a given review, which may have potentially biased the assessments.

Introduction

The care of patients with cancer continues to be a clinical research priority as documented by an increasing number of publications of different types including systematic reviews (SRs). In fact, in recent years, oncology has been the medical discipline with the highest number of publications and the numbers continue to rise.[1] The large number of oncology-related research studies poses a tremendous challenge for patients, healthcare providers, and health policymakers alike when seeking to stay abreast of a particular oncologic topic. SRs follow reproducible methods to identify relevant studies for a given question, apply pre-defined and explicit eligibility criteria, perform assessments of the validity of findings, and systematically present the results. In this context, SRs can be helpful in summarizing the current best evidence for a particular clinical question to support both individual decision-making and in serving as the basis for clinical practice guidelines. [2 3] Cochrane is widely known for having developed many of the methodological standards based on which SRs should be conducted. These standards are specified in the 2016 updated Methodological Expectations of Cochrane Intervention Reviews (MECIR). However, a large number of oncology-related SRs are currently published by clinical journals, high-impact medical journals, oncology focused journals, as well as subspecialty journals. As the number of SRs has steadily increased over the past two decades, their methodological rigor has been drawn into scrutiny.[4-6] To date, no study has formally assessed the methodological quality of oncology-related SRs which assume such a prominent place in the medical literature.

In this study, we therefore sought to formally assess the methodological quality, type, content, and citation rates of oncology related SRs, comparing SRs published in high-impact medical journals with those published in the Cochrane Database of SRs (CDSR).

Methods

The design and eligibility criteria of this project were based on an a priori written protocol. Study reporting is provided in accordance with the PRISMA statement. However, as a methodology-focused review, it was not eligible for a registration in the International Prospective Register Of Systematic Reviews (PROSPERO).

Patient involvement:

Given its methodologic focus, we did not evaluate patient-related outcomes. Therefore, we also chose not to involve patients' input in its design. However, the clear intent of this study is to indirectly benefit the welfare of patients by promoting the development and dissemination of high quality systematic reviews.

Eligibility criteria:

We selected all Cochrane reviews that examined questions related to oncology. We furthermore identified all cancer related SRs published in the highest impact medical journals, as defined by the InCites ™ Journal Citation Report® 2014, from the same time period via an electronic database search. To reflect contemporary reviews, we chose the five year period between January 2011 and May 2016 as the study timeframe. We did not apply restrictions with regards to study design or meta-analytic methods, and also included SRs without a meta-analysis. We broadly included studies related to all types of cancer.

The ten journals with the highest impact factors that published SRs on cancer topics were: *A Cancer Journal for Clinicians, New England Journal of Medicine, The Lancet, JAMA, Lancet Oncology, Journal of Clinical Oncology, The BMJ, Nature Reviews Clinical Oncology,*

Journal of the National Cancer Institute, and *Cancer Research*. We did not apply any language restrictions, however the selected journals published exclusively in English. We excluded SRs with a methodological focus. For our examination, we used the original English version of each Cochrane review (given that foreign language translation exists for many Cochrane reviews). In cases where one or more updates of previously published Cochrane reviews existed, we based our assessment on the most recently published version within the defined timeframe.

Study identification and selection

We identified all cancer-related Cochrane reviews in the CDSR from January 2011 to May 2016 using the built in "Browse by topic" database function with the options "Cancer" and "Stage: Review." In a parallel step, we conducted a comprehensive literature search of SRs published in the ten highest-impact journals from the same time-period on June 1st, 2016. An information specialist developed the search strategy for MEDLINE using the following search terms: Cancer, leukaemia, tumor, tumour, leukemia, lymphoma, myeloma, solid, neoplasm, meta-analysis, systematic review, publication dates: 2011 to 2016. We used the following MeSH terms: Neoplasm by Histologic Type and Neoplasms by Site. The full search strategy is provided in the *appendix*. Two authors independently (MG, VN) and in duplicate performed title and abstract screening, full text screening, and ultimately, selection of reviews to be included. We resolved discrepancies by discussion with one of two other authors (NS, PD).

Quality assessment

We evaluated methodological quality with the Assessment of Multiple Systematic Reviews (AMSTAR) checklist, by Shea, et al. [7] The checklist consists of 11 items and was

specially developed to assess the methodological quality of SRs and meta-analyses. In cases where AMSTAR combined several items into one criterion, we separated these out into 20 individual items for the sake of transparency but readjusted them into single items for the AMSTAR scoring. A complete list of items can be found in the *appendix*; answer options were "yes," "no," and "not applicable." Methods like sensitivity- and subgroup-analyses, or funnel plots for the assessment of publication bias require a minimum quantity of studies. For example, meaningful interpretations of funnel plots require a threshold of at least ten studies.[8] In SRs where there was evidence that these secondary analyses were planned, but not be meaningfully conducted, this criterion was rated as fulfilled. Two authors (MG, VN) performed the quality assessments independently and in duplicate. We resolved disagreements by discussion and with a third author (NS, PD).

Data extraction and extracted items

The included studies were then reviewed in detail as part of a clinical content analysis. We extracted the review type, the study design of the included studies, and review question (e.g. therapeutic, diagnostic, or prognostic) of included studies. We chose the following items to reflect the review content: Cancer type (e.g. breast, lung, colorectal, but also "cancer in general", "mixed" (but not in general) and "other" (e.g. liver metastases or male breast cancer), intervention (e.g. chemotherapy, "new drug" (targeted therapies, such as monoclonal antibodies and small molecules)), radiotherapy, surgery, supportive (e.g. interventions for cancer-related pain, rehabilitation after cancer treatment, interventions for depression in cancer patients, or adjuvant bisphosphonate treatment for cancer patients), or not applicable (if prognostic, diagnostic or epidemiological review question), population (adults, children or both), the number of included studies, and the number of included

patients. A complete list of the 17 criteria can be found in the *appendix*. To ensure the completeness of our assessment we obtained and formally considered any additional information from all (online) supplements and appendices. Two authors (MG, VN) independently extracted this data using a previously piloted form. The data extraction form was designed a priori with consensus of four authors (MG, VN, NS, PD). Discrepancies were once again resolved through discussion and third author arbitration if necessary (NS, PD).

Citations

We gathered the citation counts for both Cochrane reviews and high-impact journal reviews using the Clarivate Analytics Web of Science database. Citations counts were assessed on February 15th, 2017 by two authors independently (AW, MG). For updates of Cochrane reviews, we considered the citations of the respective update(s) and added citations from the original review, as long as the original review and any updates were published within the predefined timeframe of our study.

Data synthesis and analysis

For dichotomous variables, we determined rates, and for continuous variables, we calculated median and interquartile range (IQR), or mean and range. To compare the quality of both groups, we used risk ratios and the corresponding 95% confidence intervals. We defined an event as fulfilling a given quality indicator and have presented this data in forest plots. All statistical analyses were undertaken using Review Manager Version 5.3.

Results

Search results

As shown in the study flowchart (Figure 1), our search for oncology-related Cochrane reviews identified 412 records, of which 346 were determined to be cancer related and appropriate according to our selection criteria. Our electronic database search for high-impact SRs identified 738 records, of which 215 were ultimately included, excluding seven reviews at the full-text stage which focused on methodological issues (Figure 2). [9-15] The references of the included articles are provided in the *online appendix*.

Quality

In general, reviews published by Cochrane met each quality criterion to a greater extent than reviews published in high-impact journals (Figure 3). Cochrane reviews were more likely to report an a priori design, including the definition of the review question and a planned inclusion and exclusion criteria before conducting the review (both with a risk ratio of 3.89; 95% confidence interval (CI) 3.10 to 4.88) (AMSTAR Item 1). Differences also existed in the inclusion of unpublished and non-English literature; Cochrane reviews were more likely to include unpublished (risk ratios (RR) 3.52 (95% CI 2.84 to 4.37) and non-English studies) (RR 3.23 (95% CI 2.64 to 3.95)) (Item 4). Included studies were listed relatively equally between the two (RR 1.10; 95% CI 1.05 to 1.14) comparators, whereas a list of excluded studies, at least those rejected in the course of full-text screening, were provided almost nine times more often by Cochrane reviews (RR 8.80; 95% CI 6.06 to 12.78) (Item 5). Further, a quality assessment of the included studies (using tools such as Cochrane's Risk of Bias, the Jadad scale, or the Newcastle-Ottawa scale) were undertaken over twice as frequently in Cochrane reviews (RR 2.17; 95% CI 1.88 to 2.50) (Item 7). A meta-analysis was

conducted in 67% (227/346) of Cochrane reviews and in 80% (173/215) of high-impact journal SRs. A sensitivity analysis based on study quality or risk of bias was more commonly reported in Cochrane reviews (RR 4.17; 95% CI 3.07 to 5.67). Almost 23% (53/227) of Cochrane reviews planned to undertake, but did not perform sensitivity-analyses due to an insufficient number of included studies, the inclusion of high risk of bias studies only, or unclear information regarding study quality. Formal assessments of potential publication bias like funnel plots were undertaken or planned about twice as frequently among reviews produced by Cochrane (RR 1.98; 95% CI 1.63 to 2.41) than in SRs published in high impact journals. However, 47.3% (107/226) of Cochrane reviews and 1.7% (3/173) of reviews from high-impact journals planned, but could not perform such assessments due to an insufficient number of included studies (AMSTAR Item 10). The vast majority of SRs both in Cochrane reviews and high-impact journals disclosed potential conflicts of interest of the systematic review authors (RR 1.01; 95% CI 1.00 to 1.03). However, potential conflicts of interest of the trials included in the SRs were reported more frequently by Cochrane reviews than by SRs in high-impact journals; with Cochrane reviews being more than four times as likely to provide this information (RR 4.30; 95% CI 2.56 to 7.20) (Item 11).

Characteristics of included SRs

With regards to geographical origin, the largest proportion of Cochrane reviews originated from Europe (67.3%; 233/346) and relatively infrequently originated from North America (7.5%; 26/346); meanwhile, high-impact journal SRs were as likely to come from Europe (44.2%; 95/215) or North America (40.9%; 88/215; Table 1). Cochrane reviews were much less likely to use individual patient data (IPD) (RR 0.03; 95% CI 0.01 to 0.09) compared to aggregate study-level data. The majority of Cochrane reviews used the latter (95.7%;

331/346), with only three (0.9%; 3/346) including individual patient data exclusively, and 12 (3.5%; 12/346) using both types of data. SRs from high-impact journals were also primarily based on study level data (68.4%; 147/215), but a much larger proportion used IPD (31.2%; 67/216). Network meta-analyses were uncommon among both Cochrane reviews (0.6%; 2/346) and high-impact SRs (2.8%; 6/215).

Cochrane reviews predominantly investigated therapeutic (89%; 308/346) questions. Among SRs from high-impact journals, there were also a large number of prognostic reviews (37.2%; 80/215) in addition to therapeutic reviews (41.9%; 90/215; Figure 4). Overall, Cochrane reviews were less likely to include non-randomised controlled trials (RR 0.04; 95% CI 0.02 to 0.09). Therapeutic reviews published in the CDSR primarily included RCTs in 78.6% (242/308) or both RCTs and non-RCTs in 21.1% (65/308). High-impact journal reviews assessing therapeutic questions were primarily based on RCTs (58.9% (53/90)), with only 26.7% (24/90) based on non-RCTs.

Content of included SRs

91.9% (318/346) of the Cochrane reviews and 70.2% (151/215) high-impact journal SRs focused on adult study populations. Only 7.5% (26/346) of SRs from the CDSR and 2.8% (6/215) of reviews from high-impact journals focused solely on paediatric patients.

The largest group of Cochrane reviews addressed general cancer topics (for example: supportive measures for patients receiving cytotoxic chemotherapy) not limited to a specific type of disease (18.8 %; 65/346), followed by SRs concerning hematological malignancies (12.4%; 43/346), and breast cancer (8.4%; 29/346; Figure 5). Among SRs published in high-

impact journals, general cancer topics was also the main category followed by breast cancer in 21.4% (47/215) and colorectal cancer in 7.9% (17/215).

SRs published in Cochrane most commonly examined supportive care interventions (40.3%; 126/313), followed by chemotherapy (20.1%; 63/313), and surgery (16.7%; 49/313; Figure 6). Reviews in high-impact journals, on the other hand, predominantly evaluated specific chemotherapy regimens (25.3%; 23/91), new drugs (18.7%; 17/91), and supportive care interventions (18.7%; 17/91).

Overall, Cochrane reviews included fewer studies per review than high-impact journal SRs (median: 6 studies (IQR: 2-13) compared to 18 (18-38.8)) and fewer patients (1020 (194.5-2845) compared to 7730 (3288-29.423)). About 11.3% (39/346) of Cochrane SRs were so-called “empty reviews”, meaning the authors could not identify eligible studies to include in their review. Furthermore, 35 (10.1%) reviews retrieved from the CDSR included only one study. In contrast, none of the SRs in high-impact journals were empty or contained only a single study.

Citations

Cochrane reviews were cited considerably less frequently than SRs published in high-impact medical journals. The mean number of citations for Cochrane reviews was 6.92, ranging from 0 to 143. High-impact journal SRs had a mean of 74.45 citations with a range from 0 to 652.

Discussion

Principal findings

This methodological assessment found that Cochrane reviews were conducted with greater methodological rigor than SRs published in high-impact journals but were cited less frequently. The largest gap in terms of methodological quality with regards to an individual AMSTAR criterion was the reporting of excluded studies, which was met by all Cochrane reviews and only 11.2% (24/215) of SRs published by high-impact journals. Other major differences relate to the reporting of possible conflicts of interest of included studies, the existence of an a priori design, the conduct of sensitivity analyses for study quality of included studies, and the inclusion of non-published studies. High-impact SRs were more likely to be based on IPD, include non-RCTs and address questions other than therapy, namely prognosis. SRs that included only one or no included studies were published exclusively in the Cochrane Library, and not in high-impact journals.

Strengths and weaknesses of this systematic review

We performed this study based on an a priori protocol, a comprehensive search strategy, and data abstraction in duplicate, which lends strength to the validity of our findings. In addition, we performed a clinical content analysis comparing the two groups of SR sources. The reliability of this work was ensured through adherence to the review methods proposed by PRISMA and Cochrane. Our quality assessment was based on AMSTAR, an instrument previously validated for the assessment of SRs from RCTs which represented the best available tool at the time when we planned and conducted this review.[16 17] An updated version of AMSTAR has only recently become available. [18]

Given its focus on methodological quality, this study is unable to explain the missing link between the high methodological quality of Cochrane reviews and relatively low citation rates. Potential explanations may relate to the clinical topic areas, and too great a focus on evidence from RCTs, which has long been a hallmark of Cochrane reviews. In addition, Cochrane reviews that include none ("empty reviews") or only one study are less likely to provide newsworthy results and yield high citation rates.

The Cochrane Library permits co-publication of Cochrane reviews in other journals, which is however subject to formal pre-approval. A large number of co-published reviews could have potentially biased our results, though we identified only two reviews with this issue; this this concern is only of minor relevance.[19 20]

Strengths and weaknesses in relation to other systematic reviews

In 2016, an assessment of cross-sectional SRs was published which included a similar comparison of Cochrane and non-Cochrane reviews. [5] This assessment was cross-disciplinary and not limited to cancer alone. It comprised of SRs published during a one month period in 2014, and only 3% (9/300) of the total assessed SRs came from journals with an impact factor exceeding ten. Most of the randomly selected SRs and Cochrane reviews investigated therapeutic questions. Similar to our study, Cochrane reviews were more likely to fulfil the important methodological criteria such as protocol availability, the inclusion of unpublished and grey literature, an electronic data-search in more than two databases, data extraction and study selection performed in duplicate, or the assessment of study quality. Findings were also similar with regards to the proportion of reviews that did not perform a sensitivity analysis based on study quality. [5] Another similar study by Moher et al. documented improved reporting over a 10 year time frame.[4] A variety of other reports, including

assessments in other medical research fields have identified similar deficiencies in the quality of SRs but none of them have specifically focused on oncology-related reviews.[6 16 21-26]

Meaning of this methodological systematic review: explanations, implications and further research

Our methodological assessment highlights the major differences that exist among published SRs in oncology. Users of the medical literature should therefore not assume that SRs are equivalent in their design, methodological rigor, or validity of their conclusions. Quality criteria for SRs are well established; one key criterion is that of an a priori protocol which governs all aspects of the review process to prevent selective or biased reporting and avoid duplicate publication.[27-30] Registration of protocols with platforms such as PROSPERO can aid in holding SRs accountable in this regard; some journals have made this mandatory.[31] Deficits in the disclosure of excluded studies, for example, narrow the transparency of study selection, while absence of sensitivity analyses impede readers' accessibility of the findings against the background of study quality. Conflicts of interest may also play a role in the heterogeneity of published SRs.

A practical reason for differences in the reporting quality between Cochrane reviews and high-impact medical journals may lie in the limited space for reporting provided in printed medical journals. A recent assessment of meta-analyses of surgical interventions supports the assumption of the negative association between limited publication space and completeness of reporting. [25] Cochrane does not impose space restrictions and as such Cochrane SR authors have more freedom to provide complete reporting. However, given that most journals now offer the opportunity to provide additional e-content on the

internet, there should be fewer reasons for less than complete transparency. In this assessment, we took care to include all available content, including online supplementary tables and appendices in our assessment. Published Cochrane reviews typically also undergo a more rigorous development process that includes the compulsory publication of a protocol that has previously undergone internal editorial review and external peer review as specified in the organization's MECIR policy. This may be the main reason why Cochrane reviews are much more likely to meet more of the requirements of transparent reporting checklists. [1 7 32 33] Journal editors should similarly mandate strict adherence to PRISMA and other reporting guidelines.

Given the considerable investment of resources that goes into development of high quality Cochrane reviews, their relatively low impact is a concern. It appears critically important that Cochrane editors take greater initiative at directing review authors to topics where the greatest clinical interest lies.

This work demonstrates the need to critically assess SRs prior to using their evidence. For clinicians, the *Users' Guide to the Medical Literature* by Murad, et al. [30] provides a practical framework for assessing the validity, impact and applicability of SRs. For researchers and policy-makers aside from AMSTAR, the recently introduced ROBIS tool allows to comprehensively evaluate possible risk of bias in SRs at the review level.[34] At present it covers SRs with interventional, diagnostic, prognostic, and etiologic review questions and involves a three domain appraisal of the relevance of the respective review, an evaluation of possible risks of bias during the review process, and a concluding judgment of overall risk of bias of the review findings. [34]

Conclusion

Cancer-related SRs that are published in the CDSR demonstrate higher adherence to methodological and reporting standards than cancer-related SRs published in high-impact medical journals but are cited less frequently. Our assessment underscores the importance of performing a critical appraisal of SRs before including their evidence into guideline development or making individual clinical decisions.

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Contributors: MG designed the data collection tools and analysis, selected studies, analysed and extracted data, and drafted and revised the paper. VN designed the data collection tools and analysis, selected studies, analysed and extracted data, and drafted and revised the paper. AW extracted and analysed data and revised the paper. PD initiated the project, designed the data collection tools and analysis, selected studies, monitored data collection and analysis, and revised the paper. NS initiated the project, designed the data collection tools and analysis, selected studies, monitored data collection and analysis, and revised the paper. All authors approved the final version of the article. All authors, external and internal, had full access to all of the data (including statistical reports and tables) in the study and can take responsibility for the integrity of the data and the accuracy of the data analysis.

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Competing interests: All authors have completed the ICMJE uniform disclosure form at www.icmje.org/coi_disclosure.pdf and declare: MG, AW and NS are part of the Cochrane Haematological Malignancies Group, PD is part of the Cochrane Urology Group. Further they declare: No other support from any organisation for the submitted work; no financial relationships with any organisations that might have an interest in the submitted work in the previous three years; no other relationships or activities that could appear to have influenced the submitted work.

Ethical approval: Not required

Data sharing: No additional data available

Transparency: We affirm that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned have been explained.

Figure legends

Figure 1. PRISMA flow diagram of Cochrane reviews

Figure 2. PRISMA flow diagram of high-impact journal SRs

Figure 3. Forrest plot comparing to what extent Cochrane reviews and SRs published in high-impact journals meet criteria for methodological quality

Figure 4. Distribution of Cochrane reviews and high-impact journal SRs by review question

Figure 5. Distribution of Cochrane reviews and high-impact journal SRs by disease

Figure 6. Distribution of Cochrane reviews and high-impact journal SRs by intervention

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Table 1: Baseline characteristics of the included Cochrane reviews and high-impact journal SRs

	Cochrane	High-impact journals							
	Cochrane reviews (n=346)	***Total high-impact journal SRs (n=215)***	J Natl Cancer Inst (n=56)	J Clin Oncol (n=56)	Lancet Oncology (n=53)	The BMJ (n=22)	Lancet (n=14)	JAMA (n=12)	CA Cancer J Clin (n=1)	Cancer Research (n=1)
Year first published (Number of SR (%))										
2011	45 (13.1)	45 (20.9)	9 (16.1)	14 (25)	13 (24.5)	2 (9.1)	4 (28.6)	3 (25)		
2012	60 (17.3)	50 (23.2)	20 (35.7)	11 (19.6)	11 (20.8)	4 (18.2)	1 (7.1)	3 (25)		
2013	80 (23.1)	31 (14.4)	7 (12.5)	8 (14.3)	8 (15.1)	5 (22.7)	2 (14.3)	1 (8.3)		
2014	59 (17.1)	51 (23.7)	11 (19.6)	10 (17.9)	15 (28.3)	7 (31.8)	4 (28.6)	4 (33.3)		
2015	69 (19.9)	32 (14.9)	6) (10.7)	11 (19.6)	5 (9.4)	4 (18.2)	3 (21.4)	1 (8.3)	1 (100)	1 (100)
2016	33 (9.5)	6 (2.8)	3 (5.4)	2 (3.6)	1 (1.9)					
Region (Number of SR (%))										
Europe	233 (67.3)	95 (44.2)	14 (25)	20 (35.7)	34 (64.2)	12 (54.5)	13 (92.9)	1 (8.3)	1 (100)	
North America	26 (7.5)	88 (40.9)	33 (58.9)	27 (48.2)	10 (18.9)	6 (27.3)	1 (7.1)	10 (83.3)		1 (100)
Asia	49 (14.2)	16 (7.4)	6 (10.7)	3 (5.4)	3 (5.7)	3 (13.6)		1 (8.3)		
Australia/ New Zealand	19 (5.5)	14 (6.5)	2 (3.6)	6 (10.7)	6 (11.3)					
South America	13 (3.8)	1 (0.5)	1 (1.8)							
Africa	6 (1.7)	1 (0.5)				1 (4.5)				
Review type (Number of SR (%))										
Study-level	331 (95.7)	147 (68.4)	39 (69.6)	40 (71.4)	35 (66)	19 (86.4)	1 (7.1)	11 (91.7)	1 (100)	1 (100)

	Cochrane	High-impact journals								
	Cochrane reviews (n=346)	***Total high-impact journal SRs (n=215)***	J Natl Cancer Inst (n=56)	J Clin Oncol (n=56)	Lancet Oncology (n=53)	The BMJ (n=22)	Lancet (n=14)	JAMA (n=12)	CA Cancer J Clin (n=1)	Cancer Research (n=1)
data										
IPD	3 (0.9)	67 (31.2)	17 (30.4)	15 (26.8)	18 (34)	3 (13.6)	13 (92.9)	1 (8.3)		
Both	12 (3.5)	1 (0.5)		1 (1.8)						
Network Meta-Analysis (Number of SR (%))	2 (0.6)	6 (2.8)	3 (5.4)		3 (5.7)					
Study type (Number of SR (%))										
RCT	264 (76.3)	75 (34.9)	15 (26.8)	21 (37.5)	14 (26.4)	7 (31.8)	12 (85.7)	5 (41.7)	1 (100)	
non-RCT	5 (1.4)	85 (39.5)	27 (48.2)	16 (28.6)	27 (50.9)	12 (54.5)	1 (7.1)	2 (16.7)		
Both	77 (22.3)	46 (21.4)	9 (16.1)	19 (33.9)	9 (17)	3 (13.6)	1 (7.1)	5 (41.7)		
Unclear		9 (4.2)	5 (8.9)		3 (5.7)					1 (100)
Population (Number of SR (%))										
Adult	318 (9.9)	151 (70.2)	39 (69.6)	43 (76.8)	32 (60.4)	14 (63.6)	13 (92.9)	9 (75)	1 (100)	
Paediatric	26 (7.5)	6 (2.8)	1 (1.8)	1 (1.8)	4 (7.5)					
Both	2 (0.6)	22 (10.2)	5 (8.9)	6 (10.7)	7 (13.2)	4 (18.2)				
Unclear		36 (16.7)	11 (19.6)	6 (10.7)	10 (18.9)	4 (18.2)	1 (7.1)	3 (25)		1 (100)
Included studies (Median (IQR))	6 (2-13)	18 (10-38,8)	20 (12-43.8)	16 (9-36.3)	24 (12.8-44.8)	16 (9.6-26.5)	16 (25-9.8)	16.5 (10.3-24.8)	14	37

	Cochrane	High-impact journals								
	Cochrane reviews (n=346)	***Total high-impact journal SRs (n=215)***	J Natl Cancer Inst (n=56)	J Clin Oncol (n=56)	Lancet Oncology (n=53)	The BMJ (n=22)	Lancet (n=14)	JAMA (n=12)	CA Cancer J Clin (n=1)	Cancer Research (n=1)
Included patients (Median (IQR))	1020 (194.5-2845)	7730 (3288-29423)	8216 (3288-35568)	4758,5 (184.5-11091.8)	4600 (3033-21137)	117597 (10903-890992.3)	21471.5 (13287.5-45195.8)	12813.5 (4075.5-48067.3)	3377	Not reported
Citations (Median (IQR))	3 (1-7)	46 (18,5-86,5)	30.5 (9.8-55.3)	48,5 (18-70.3)	40 (22-97)	40 (15-80.3)	157 (54-351.8)	101 (45.3-155.8)	8	15

SR= systematic review, IPD= Individual Patient Data, J Natl Cancer Inst= Journal of the National Cancer Institute, J Clin Oncol= Journal of Clinical Oncology, CA Cancer J Clin= A Cancer Journal for Clinicians, Cancer Res= Cancer Research, RCT=randomised controlled trial, IQR= interquartile range

Appendix

Appendix table 1: Search strategy for high-impact journals SRs

Search	
#1	Search ((((((((((((("Cancer Research"[Journal]) OR "Ca-A Cancer Journal for Clinicians"[Journal]) OR "Nature reviews. Clinical oncology"[Journal]) OR "Clinical cancer research : an official journal of the American Association for Cancer Research"[Journal]) OR)) OR ((((("BMJ (Clinical research ed.)"[Journal]) OR "The Lancet. Oncology"[Journal]) OR "JAMA"[Journal]) OR "The New England journal of medicine"[Journal]) OR "Journal of clinical oncology : official journal of the American Society of Clinical Oncology"[Journal]) OR "Annals of oncology : official journal of the European Society for Medical Oncology / ESMO"[Journal]) OR "Journal of the National Cancer Institute"[Journal]) OR "Lancet (London, England)"[Journal]))))))))))))
#2	Search ((((((((((((((((((((((((((((NEOPLASMS BY HISTOLOGIC TYPE[MeSH Terms]) OR NEOPLASMS BY SITE[MeSH Terms]) OR neoplas*) OR tumor*) OR tumour*) OR ((Krebs* or cancer*))) OR malignan*) OR ((carcino* or karzino* or karzinom*))) OR sarcom*) OR (leukem* or leukaem*)) OR lymphom*) OR melano*) OR metastas*) OR ((mesothelio* or mesotelio*))) OR carcinomatos*) OR ((gliom* or glioblastom*))) OR osteo*sarcom*) OR ((blastom* or neuroblastom*))))))))))))))
#3	Search (((((systematic review[Title/Abstract]) OR (((((meta-

	analys*[Title/Abstract]) OR metaanalys*[Title/Abstract]))))))))
#4	Search ((#1 and #2 and #3))
#5	Search (#1 and #2) Filters: Meta-Analysis; Systematic Reviews
#6	Search (#4 or #7) Filters: Publication date from 2011/01/01 to 2016/05/31

Appendix table 2: Extracted items

Item	Extracted	Example
1.	Author	
2.	Title	
3.	Journal	Cochrane, A Cancer Journal for Clinicians, New England Journal of Medicine, The Lancet, JAMA, Lancet Oncology, Journal of Clinical Oncology, The BMJ, Nature Reviews Clinical Oncology, Journal of the National Cancer Institute, Cancer Research
4.	Year last updated	2011-2016
5.	Year first published	2011-2016
6.	Cochrane group	
7.	Region of corresponding author	Africa, Asia, Australia/ New Zealand, Europe, North America, South America
8.	Review type	SR based on trial-level data, Individual Patient Data SR, Both
9.	Network Meta-Analysis	Yes, No
10.	Included study type	RCTs, non-RCTs, Both
11.	Question type	Diagnosis, Epidemiology, Prevention, Prognosis, Screening, Therapy

Item	Extracted	Example
12.	Disease	Bladder, bones (incl. spine), brain (incl. CNS), breast, cancer in general, cervical, colorectal, endometrial, oesophagus, gastric, haematological (leukaemia, lymphoma, myeloma), head and neck, lung, melanoma, mixed (but not general, other (e.g. male breast cancer, liver metastases), ovarian, pancreas, prostate, renal, uterus
13.	Intervention	Behavioural (e.g. exercise, diet, smoking), chemotherapy, mixed interventions, "new drug" (targeted therapy and monoclonal antibodies), radiotherapy, supportive, surgery, thermal (e.g. hyperthermia, crytotherapy), not applicable (if diagnostic, prognostic, preventive, epidemiologic, screening)
14.	Population	Adult, paediatric, both
15.	Number of included studies	

Item	Extracted	Example
16.	Number included patients	

Appendix table 3: Extracted quality indicators

Item	AMSTAR	This work
1.	Was an 'a priori' design provided	Was the review question established before the conduct of the review?
		Were the in- and exclusion criteria defined before the conduct of the review?
2.	Was there duplicate study selection and data extraction?	Was the study selection and data-extraction undertaken by two independently working authors?
		Was the consensus procedure described?
		Was the interobserver-agreement (quantitatively) assessed?
3.	Was a comprehensive literature search performed?	Were at least two electronic databases searched?
		Were the years included in the searches reported?
		Were the database searches supported by other sources?
4.	Was the status of publication	Were reviews irrespective of publication

Item	AMSTAR	This work
	(i.e. grey literature) used as an inclusion criterion?	status included?
		Were reviews in languages other than English included?
5.	Was a list of studies (included and excluded) provided?	Was a list of included studies provided?
		Was a list of excluded studies provided?
6.	Were the characteristics of the included studies provided?	Were study characteristic of every included study included?
7.	Was the scientific quality of the included studies assessed and documented?	Was the quality of included studies included by available tools (e.g. Cochrane's Risk of Bias, ROBINS, Newcastle-Ottawa scale)
8.	Was the scientific quality of the included studies used appropriately in formulating conclusions?	If a Meta-analysis was performed: Was the study quality included into the analysis via sensitivity- or subgroup analysis?
9.	Were the methods used to combine the findings of studies appropriate?	Was possible heterogeneity assessed?

Item	AMSTAR	This work
10.	Was the likelihood of publication bias assessed?	Was possible publication bias formally assessed?
11.	Was the conflict of interest included?	Were possible Conflicts of Interest regarding the review disclosed?
		Were possible Conflicts of Interest of the included studies reported?

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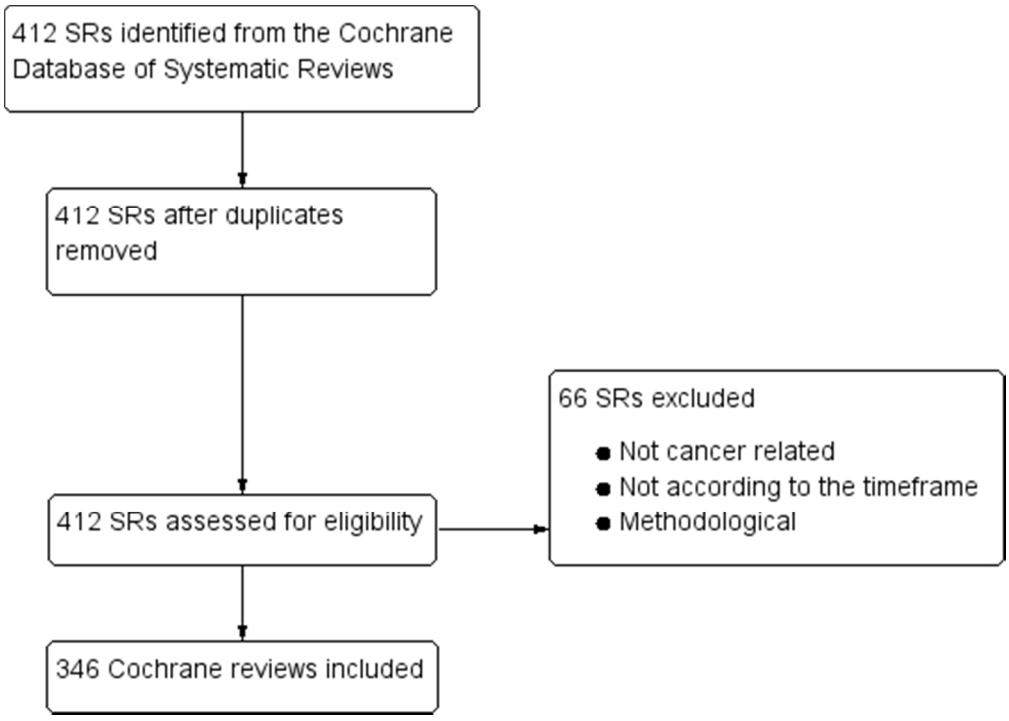

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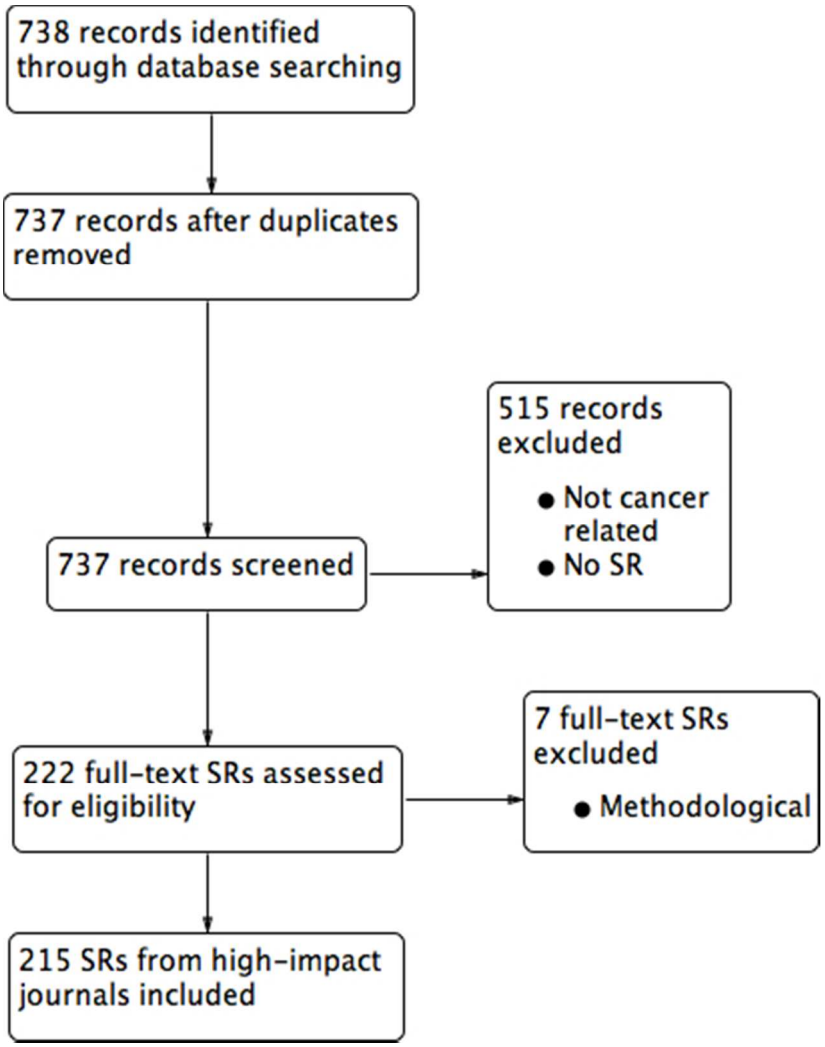

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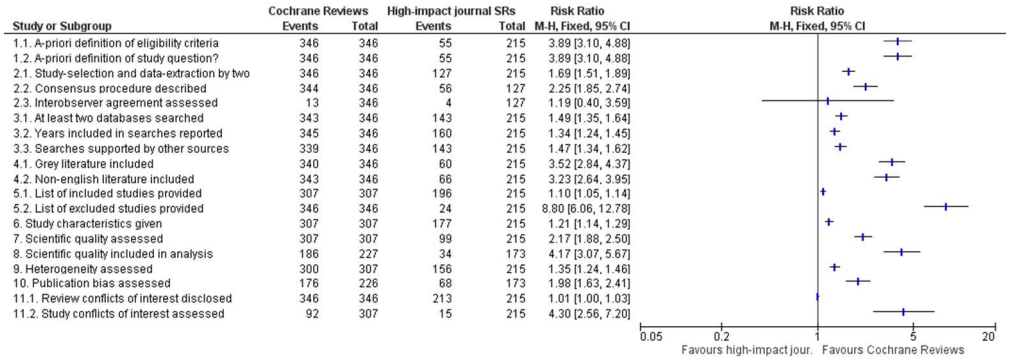

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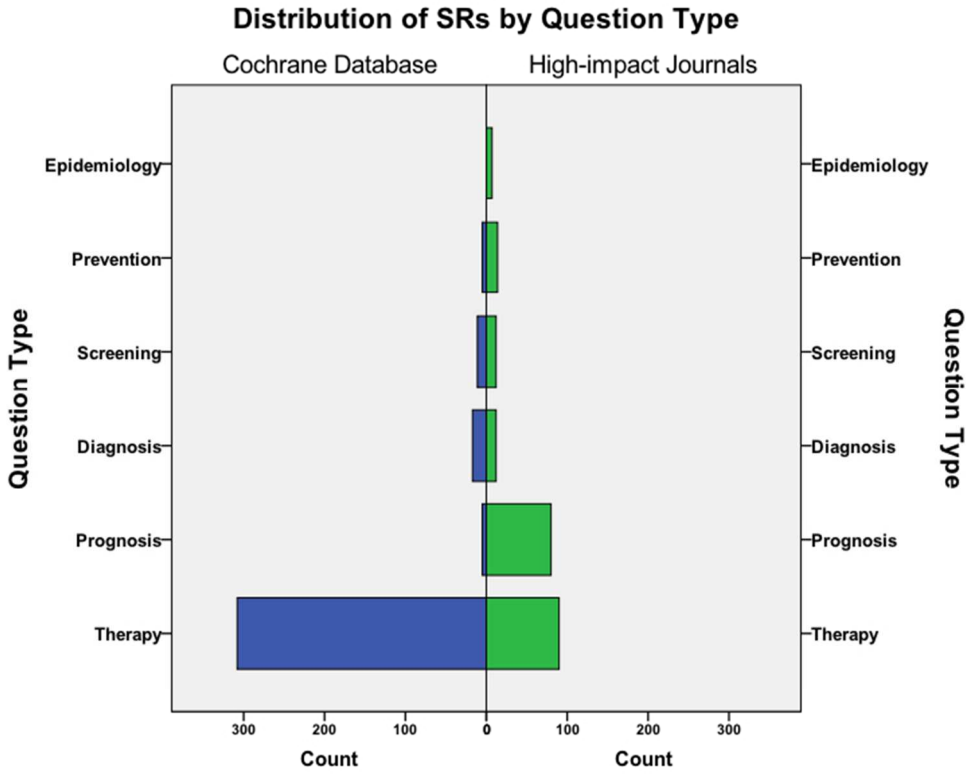

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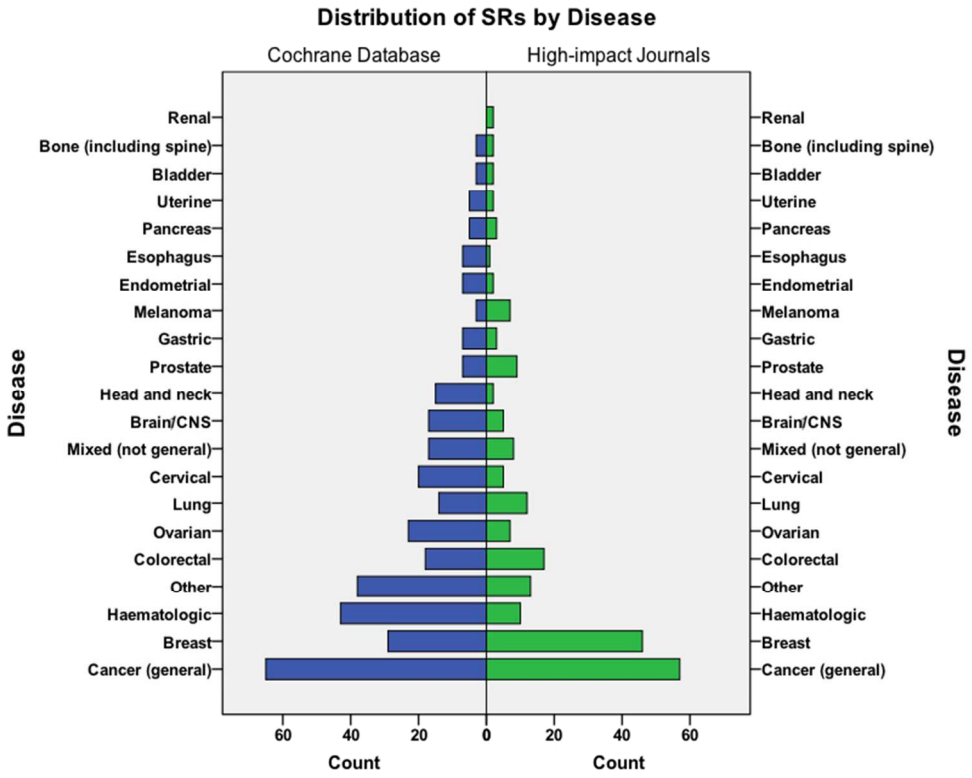

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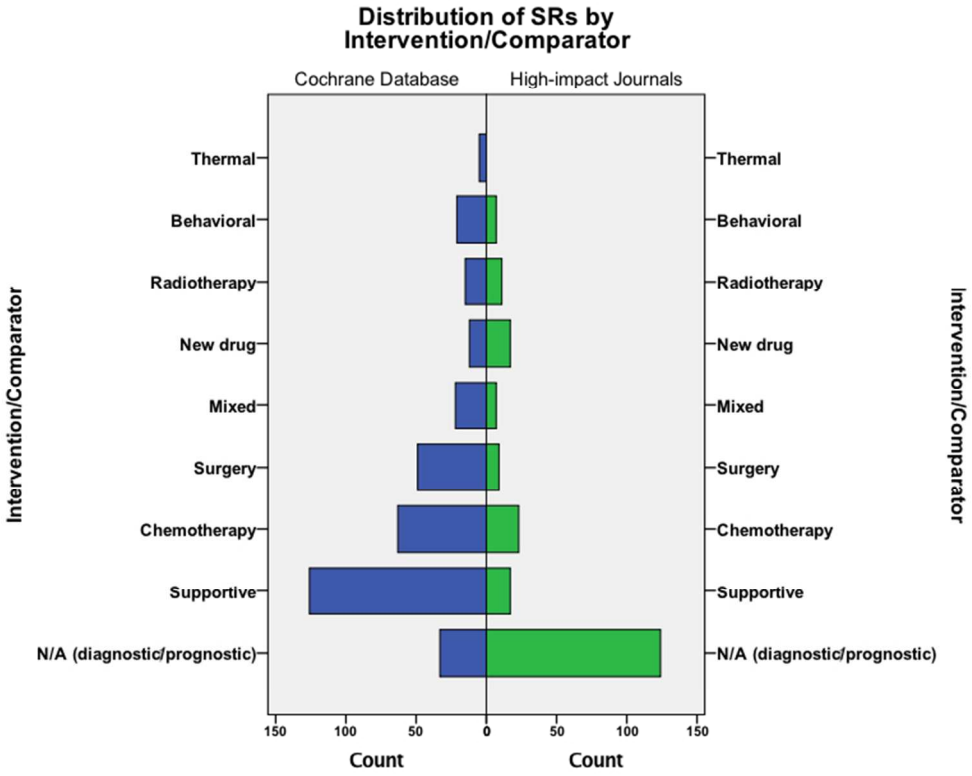

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PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	2-3
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	4
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	4
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	5
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	5
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	6
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	6 and Appendix
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	6
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	7
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	7
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	7-8
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	8
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	8

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	NA
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	NA
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	9 and flow diagrams
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	NA
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	NA
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	9-12 and forest plot
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	NA
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	NA
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	NA
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	13-16
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	13-14
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	15-16
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	18

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097

PRISMA 2009 Checklist

BMJ Open

A Systematic Assessment of Cochrane Reviews and Systematic Reviews Published in High-Impact Medical Journals Related to Cancer

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2017-020869.R1
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Primary Subject Heading:	Research methods
Secondary Subject Heading:	Oncology
Keywords:	methodological systematic review, AMSTAR, quality assessment

A Systematic Assessment of Cochrane Reviews and Systematic Reviews Published in High-Impact Medical Journals Related to Cancer

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Abstract

Objective: To compare cancer-related systematic reviews (SRs) published in the Cochrane Database of SRs (CDSR) and high-impact journals, with respect to type, content, quality, and citation rates.

Design: Methodological SR with assessment and comparison of SRs and meta-analyses. Two authors independently assessed methodological quality using an Assessment of Multiple Systematic Reviews (AMSTAR)–based extraction form. Both authors independently screened search results, extracted content-relevant characteristics, and retrieved citation numbers of the included reviews using the Clarivate Analytics Web of Science database.

Data sources: Cancer-related SRs were retrieved from the CDSR, as well as from the ten journals which publish oncologic SRs and had the highest impact factors, using a comprehensive search in both the CDSR and MEDLINE.

Eligibility criteria for selecting studies: We included all cancer-related SRs and meta-analyses published from January 2011 to May 2016. Methodological SRs were excluded.

Results: We included 346 applicable Cochrane reviews and 215 SRs from high-impact journals. Cochrane reviews consistently met more individual AMSTAR criteria, notably with regards to an a-priori design (RR 3.89; 95% CI 3.10 to 4.88), inclusion of the grey literature and trial registries (RR 3.52; 95% CI 2.84 to 4.37) in their searches, and the reporting of excluded studies (RR 8.80; 95% CI 6.06 to 12.78). Cochrane reviews were less likely to address questions of prognosis (RR 0.04; 95% CI 0.02 to 0.09), use individual patient data (RR 0.03; 95% CI 0.01 to 0.09), or be based on non-randomised controlled trials (RR 0.04; 95% CI 0.02 to 0.09). Citation rates of Cochrane reviews were notably lower than those for high-

impact journals (Cochrane reviews: mean number of citations 6.52 (range 0 to 143); High-impact journal SRs: 74.45 (0 to 652)).

Conclusions: When comparing cancer-related SRs published in the CDSR versus those published in high-impact medical journals, Cochrane reviews were consistently of higher methodological quality, but cited less frequently.

Strengths and limitations of this study

-Unique cross-disciplinary comparison of systematic reviews in oncology including over 550 SRs.

-Methodological assessment using AMSTAR, a validated and widely used tool to evaluate the quality of systematic reviews.

-It was not feasible to blind the authors of this study to the source journal of a given review, which may have potentially biased the assessments.

Introduction

The care of patients with cancer continues to be a clinical research priority as documented by an increasing number of publications of different types including systematic reviews (SRs). In fact, in recent years, oncology has been the medical discipline with the highest number of publications and the numbers continue to rise.[1] The large number of oncology-related research studies poses a tremendous challenge for patients, healthcare providers, and health policymakers alike when seeking to stay abreast of a particular oncologic topic. SRs follow reproducible methods to identify relevant studies for a given question, apply pre-defined and explicit eligibility criteria, perform assessments of the validity of findings, and systematically present the results. In this context, SRs can be helpful in summarizing the current best evidence for a particular clinical question to support both individual decision-making and in serving as the basis for clinical practice guidelines. [2 3] Cochrane is widely known for having developed many of the methodological standards based on which SRs should be conducted. These standards are specified in the 2016 updated Methodological Expectations of Cochrane Intervention Reviews (MECIR). However, a large number of oncology-related SRs are currently published by clinical journals, high-impact medical journals, oncology focused journals, as well as subspecialty journals. As the number of SRs has steadily increased over the past two decades, their methodological rigor has been drawn into scrutiny.[4-6] To date, no study has formally assessed the methodological quality of oncology-related SRs which assume such a prominent place in the medical literature.

In this study, we therefore sought to formally assess the methodological quality, type, content, and citation rates of oncology related SRs, comparing SRs published in high-impact medical journals with those published in the Cochrane Database of SRs (CDSR).

Methods

The design and eligibility criteria of this project were based on an a priori written protocol. Study reporting is provided in accordance with the PRISMA statement. However, as a methodology-focused review, it was not eligible for a registration in the International Prospective Register Of Systematic Reviews (PROSPERO).

Patient involvement:

Given its methodological focus, we did not evaluate patient-related outcomes. Therefore, we also chose not to involve patients' input in its design. However, the clear intent of this study is to indirectly benefit the welfare of patients by promoting the development and dissemination of high quality systematic reviews.

Eligibility criteria:

We selected all Cochrane reviews that examined questions related to oncology. We furthermore identified all cancer related SRs published in the highest impact medical journals, as defined by the InCites ™ Journal Citation Report® 2014, from the same time period via an electronic database search. To reflect contemporary reviews, we chose the five-year period between January 2011 and May 2016 as the study timeframe. We did not apply restrictions with regards to study design or meta-analytic methods, and also included SRs without a meta-analysis. We broadly included studies related to all types of cancer.

The ten journals with the highest impact factors that published SRs on cancer topics were: *A Cancer Journal for Clinicians, New England Journal of Medicine, The Lancet, JAMA, Lancet Oncology, Journal of Clinical Oncology, The BMJ, Nature Reviews Clinical Oncology,*

Journal of the National Cancer Institute, and *Cancer Research*. We did not apply any language restrictions, however all selected journals published exclusively in English. We excluded SRs with a methodological focus. For our examination, we used the original English version of each Cochrane review (given that foreign language translation exists for many Cochrane reviews). In cases where one or more updates of previously published Cochrane reviews existed, we based our assessment on the most recently published version within the defined timeframe.

Study identification and selection

We identified all cancer-related Cochrane reviews in the CDSR from January 2011 to May 2016 using the built in "Browse by topic" database function with the options "Cancer" and "Stage: Review." In a parallel step, we conducted a comprehensive literature search of SRs published in the ten highest-impact journals from the same time-period on June 1st, 2016. An information specialist developed the search strategy for MEDLINE using the following search terms: Cancer, leukaemia, tumor, tumour, leukemia, lymphoma, myeloma, solid, neoplasm, meta-analysis, systematic review, publication dates: 2011 to 2016. We used the following MeSH terms: Neoplasm by Histologic Type and Neoplasms by Site. The full search strategy is provided in the *appendix*. Two authors independently (MG, VN) and in duplicate performed title and abstract screening, full text screening, and ultimately, selection of reviews to be included. We resolved discrepancies by discussion with one of two other authors (NS, PD).

Quality assessment

We evaluated methodological quality with the Assessment of Multiple Systematic Reviews (AMSTAR) checklist, by Shea, et al. [7] The checklist consists of 11 items and was

specially developed to assess the methodological quality of SRs and meta-analyses. In cases where AMSTAR combined several items into one criterion, we separated these out into 20 individual items for the sake of transparency but readjusted them into single items for the AMSTAR scoring. A complete list of items can be found in the *appendix*; answer options were "yes," "no," and "not applicable." Methods like sensitivity- and subgroup-analyses, or funnel plots for the assessment of publication bias require a minimum quantity of studies. For example, meaningful interpretations of funnel plots require a threshold of at least ten studies.[8] In SRs where there was evidence that these secondary analyses were planned, but could not be meaningfully conducted, this criterion was rated as fulfilled. Two authors (MG, VN) performed the quality assessments independently and in duplicate. We resolved disagreements by discussion and with a third author (NS, PD).

Data extraction and extracted items

The included studies were then reviewed in detail as part of a clinical content analysis. We extracted the review type, the study design of the included studies, and review question (e.g. therapeutic, diagnostic, or prognostic) of included studies. We chose the following items to reflect the review content: Cancer type (e.g. breast, lung, colorectal, but also "cancer in general", "mixed" (but not in general) and "other" (e.g. liver metastases or male breast cancer), intervention (e.g. chemotherapy, "new drug" (targeted therapies, such as monoclonal antibodies and small molecules)), radiotherapy, surgery, supportive (e.g. interventions for cancer-related pain, rehabilitation after cancer treatment, interventions for depression in cancer patients, or adjuvant bisphosphonate treatment for cancer patients), or not applicable (if prognostic, diagnostic or epidemiological review question), population (adults, children or both), the number of included studies, and the number of included

patients. A complete list of the 17 criteria can be found in the *appendix*. To ensure the completeness of our assessment we obtained and formally considered any additional information from all (online) supplements and appendices. Two authors (MG, VN) independently extracted this data using a previously piloted form. The data extraction form was designed a priori with consensus of four authors (MG, VN, NS, PD). Discrepancies were once again resolved through discussion and third author arbitration if necessary (NS, PD).

Citations

We gathered the citation counts for both Cochrane reviews and high-impact journal reviews using the Clarivate Analytics Web of Science database. Citations counts were assessed on February 15th, 2017 by two authors independently (AW, MG). For updates of Cochrane reviews, we considered the citations of the respective update(s) and added citations from the original review, as long as the original review and any updates were published within the predefined timeframe of our study.

Data synthesis and analysis

For dichotomous variables, we determined rates, and for continuous variables, we calculated median and interquartile range (IQR), or mean and range. To compare the quality of both groups, we used risk ratios and the corresponding 95% confidence intervals. We defined an event as fulfilling a given quality indicator and have presented this data in forest plots. All statistical analyses were undertaken using Review Manager Version 5.3.

Results

Search results

As shown in the study flowchart (Figure 1), our search for oncology-related Cochrane reviews identified 412 records, of which 346 were determined to be cancer related and appropriate according to our selection criteria. Our electronic database search for high-impact SRs identified 738 records, of which 215 were ultimately included, excluding seven reviews at the full-text stage which focused on methodological issues (Figure 2). [9-15] The references of the included articles are provided in the *online appendix*.

Quality

In general, reviews published by Cochrane met each quality criterion to a greater extent than reviews published in high-impact journals (Figure 3). Cochrane reviews were more likely to report an a priori design, including the definition of the review question and a planned inclusion and exclusion criteria before conducting the review (both with a risk ratio of 3.89; 95% confidence interval (CI) 3.10 to 4.88) (AMSTAR Item 1). Differences also existed in the inclusion of unpublished and non-English literature; Cochrane reviews were more likely to include unpublished (risk ratios (RR) 3.52 (95% CI 2.84 to 4.37) and non-English studies) (RR 3.23 (95% CI 2.64 to 3.95)) (Item 4). Included studies were listed relatively equally between the two (RR 1.10; 95% CI 1.05 to 1.14) comparators, whereas a list of excluded studies, at least those rejected in the course of full-text screening, were provided almost nine times more often by Cochrane reviews (RR 8.80; 95% CI 6.06 to 12.78) (Item 5). Further, a quality assessment of the included studies (using tools such as Cochrane's Risk of Bias, the Jadad scale, or the Newcastle-Ottawa scale) was undertaken over twice as frequently in Cochrane reviews (RR 2.17; 95% CI 1.88 to 2.50) (Item 7). A meta-analysis was

conducted in 67% (227/346) of Cochrane reviews and in 80% (173/215) of high-impact journal SRs. A sensitivity analysis based on study quality or risk of bias was more commonly reported in Cochrane reviews (RR 4.17; 95% CI 3.07 to 5.67). Almost 23% (53/227) of Cochrane reviews planned to undertake but did not perform sensitivity-analyses due to an insufficient number of included studies, the inclusion of high risk of bias studies only, or unclear information regarding study quality. Formal assessments of potential publication bias like funnel plots were undertaken or planned about twice as frequently among reviews produced by Cochrane (RR 1.98; 95% CI 1.63 to 2.41) than in SRs published in high impact journals. However, 47.3% (107/226) of Cochrane reviews and 1.7% (3/173) of reviews from high-impact journals planned but could not perform such assessments due to an insufficient number of included studies (AMSTAR Item 10). The vast majority of SRs both in Cochrane reviews and high-impact journals disclosed potential conflicts of interest of the SR authors (RR 1.01; 95% CI 1.00 to 1.03). However, potential conflicts of interest of the trials included in the SRs were reported more frequently by Cochrane reviews than by SRs in high-impact journals; with Cochrane reviews being more than four times as likely to provide this information (RR 4.30; 95% CI 2.56 to 7.20) (Item 11).

Characteristics of included SRs

With regards to geographical origin, the largest proportion of Cochrane reviews originated from Europe (67.3%; 233/346) and relatively infrequently originated from North America (7.5%; 26/346); meanwhile, high-impact journal SRs were as likely to come from Europe (44.2%; 95/215) or North America (40.9%; 88/215; Table 1). Cochrane reviews were much less likely to use individual patient data (IPD) (RR 0.03; 95% CI 0.01 to 0.09) compared to aggregate study-level data. The majority of Cochrane reviews used the latter (95.7%;

331/346), with only three (0.9%; 3/346) including individual patient data exclusively, and 12 (3.5%; 12/346) using both types of data. SRs from high-impact journals were also primarily based on study level data (68.4%; 147/215), but a much larger proportion used IPD (31.2%; 67/216). Network meta-analyses were uncommon among both Cochrane reviews (0.6%; 2/346) and high-impact SRs (2.8%; 6/215).

Cochrane reviews predominantly investigated therapeutic (89%; 308/346) questions. Among SRs from high-impact journals, there was also a large number of prognostic reviews (37.2%; 80/215) in addition to therapeutic reviews (41.9%; 90/215; Figure 4). Overall, Cochrane reviews were less likely to include non-randomised controlled trials (RR 0.04; 95% CI 0.02 to 0.09). Therapeutic reviews published in the CDSR primarily included RCTs in 78.6% (242/308) or both RCTs and non-RCTs in 21.1% (65/308). High-impact journal reviews assessing therapeutic questions were primarily based on RCTs (58.9% (53/90)), with only 26.7% (24/90) based on non-RCTs.

Content of included SRs

91.9% (318/346) of the Cochrane reviews and 70.2% (151/215) high-impact journal SRs focused on adult study populations. Only 7.5% (26/346) of SRs from the CDSR and 2.8% (6/215) of reviews from high-impact journals focused solely on paediatric patients.

The largest group of Cochrane reviews addressed general cancer topics (for example: supportive measures for patients receiving cytotoxic chemotherapy) not limited to a specific type of disease (18.8 %; 65/346), followed by SRs concerning hematological malignancies (12.4%; 43/346), and breast cancer (8.4%; 29/346; Figure 5). Among SRs published in high-

impact journals, general cancer topics was also the main category followed by breast cancer in 21.4% (47/215) and colorectal cancer in 7.9% (17/215).

SRs published in Cochrane most commonly examined supportive care interventions (40.3%; 126/313), followed by chemotherapy (20.1%; 63/313), and surgery (16.7%; 49/313; Figure 6). Reviews in high-impact journals, on the other hand, predominantly evaluated specific chemotherapy regimens (25.3%; 23/91), new drugs (18.7%; 17/91), and supportive care interventions (18.7%; 17/91).

Overall, Cochrane reviews included fewer studies per review than high-impact journal SRs (median: 6 studies (IQR: 2-13) compared to 18 (18-38.8)) and fewer patients (1020 (194.5-2845) compared to 7730 (3288-29.423)). About 11.3% (39/346) of Cochrane SRs were so-called “empty reviews”, meaning the authors could not identify eligible studies to include in their review. Furthermore, 35 (10.1%) reviews retrieved from the CDSR included only one study. In contrast, none of the SRs in high-impact journals were empty or contained only a single study.

Citations

Cochrane reviews were cited considerably less frequently than SRs published in high-impact medical journals. The mean number of citations for Cochrane reviews was 6.92, ranging from 0 to 143. High-impact journal SRs had a mean of 74.45 citations with a range from 0 to 652.

Discussion

Principal findings

This methodological assessment found that Cochrane reviews were conducted with greater methodological rigor than SRs published in high-impact journals but were cited less frequently. The largest gap in terms of methodological quality with regards to an individual AMSTAR criterion was the reporting of excluded studies, which was met by all Cochrane reviews and only 11.2% (24/215) of SRs published by high-impact journals. Other major differences relate to the reporting of possible conflicts of interest of included studies, the existence of an a priori design, the conduct of sensitivity analyses for study quality of included studies, and the inclusion of non-published studies. High-impact SRs were more likely to be based on IPD, include non-RCTs and address questions other than therapy, namely prognosis. SRs that included only one or no included studies were published exclusively in the Cochrane Library, and not in high-impact journals.

Strengths and weaknesses of this systematic review

We performed this study based on an a priori protocol, a comprehensive search strategy, and data abstraction in duplicate, which lends strength to the validity of our findings. In addition, we performed a clinical content analysis comparing the two groups of SR sources. The reliability of this work was ensured through adherence to the review methods proposed by PRISMA and Cochrane. Our quality assessment was based on AMSTAR, an instrument previously validated for the assessment of SRs from RCTs which represented the best available tool at the time when we planned and conducted this review.[16 17] An updated version of AMSTAR has only recently become available. [18]

Given its focus on methodological quality, this study is unable to explain the missing link between the high methodological quality of Cochrane reviews and relatively low citation rates. Potential explanations may relate to the clinical topic areas, and too great a focus on evidence from RCTs, which has long been a hallmark of Cochrane reviews. In addition, Cochrane reviews that include none ("empty reviews") or only one study are less likely to provide newsworthy results and yield high citation rates.

The Cochrane Library permits co-publication of Cochrane reviews in other journals, which is however subject to formal pre-approval. A large number of co-published reviews could have potentially biased our results, though we identified only two reviews with this issue; thus this concern is only of minor relevance.[19 20]

Strengths and weaknesses in relation to other systematic reviews

In 2016, a cross-sectional assessment of SRs was published which included a similar comparison of Cochrane and non-Cochrane reviews. [5] This assessment was cross-disciplinary and not limited to cancer alone. It consisted of SRs published during a one-month period in 2014, and only 3% (9/300) of the total assessed SRs came from journals with an impact factor exceeding ten. Most of the randomly selected SRs and Cochrane reviews investigated therapeutic questions. Similar to our study, Cochrane reviews were more likely to fulfil the important methodological criteria such as protocol availability, the inclusion of unpublished and grey literature, an electronic data-search in more than two databases, data extraction and study selection performed in duplicate, or the assessment of study quality. Findings were also similar with regards to the proportion of reviews that did not perform a sensitivity analysis based on study quality. [5] Another similar study by Moher et al. documented improved reporting over a 10 year time frame.[4] A variety of other reports, including

assessments in other medical research fields have identified similar deficiencies in the quality of SRs but none of them have specifically focused on oncology-related reviews.[6 16 21-26]

Meaning of this methodological systematic review: explanations, implications and further research

Our methodological assessment highlights the major differences that exist among published SRs in oncology. Users of the medical literature should therefore not assume that SRs are equivalent in their design, methodological rigor, or validity of their conclusions. Quality criteria for SRs are well established; one key criterion is that of an a priori protocol which governs all aspects of the review process to prevent selective or biased reporting and avoid duplicate publication.[27-30] Registration of protocols with platforms such as PROSPERO can aid in holding SRs accountable in this regard; some journals have made this mandatory.[31] Deficits in the disclosure of excluded studies, for example, narrow the transparency of study selection, while absence of sensitivity analyses impede the possibility of readers to assess the findings against the background of study quality. Conflicts of interest may also play a role in the heterogeneity of published SRs.

A practical reason for differences in the reporting quality between Cochrane reviews and high-impact medical journals may lie in the limited space for reporting provided in printed medical journals. A recent assessment of meta-analyses of surgical interventions supports the assumption of the negative association between limited publication space and completeness of reporting. [25] Cochrane does not impose space restrictions and as such Cochrane SR authors have more freedom to provide complete reporting. However, given that most journals now offer the opportunity to provide additional e-content on the

internet, there should be fewer reasons for less than complete transparency. In this assessment, we took care to include all available content, including online supplementary tables and appendices in our assessment. Published Cochrane reviews typically also undergo a more rigorous development process that includes the compulsory publication of a protocol that has previously undergone internal editorial review and external peer review as specified in the organization's MECIR policy. This may be the main reason why Cochrane reviews are much more likely to meet more of the requirements of transparent reporting checklists. [1 7 32 33] Journal editors should similarly mandate strict adherence to PRISMA and other reporting guidelines.

Given the considerable investment of resources that goes into development of high quality Cochrane reviews, their relatively low impact is a concern. It appears critically important that Cochrane editors take greater initiative at directing review authors to topics where the greatest clinical interest lies.

This work demonstrates the need to critically assess SRs prior to using their evidence. For clinicians, the *Users' Guide to the Medical Literature* by Murad, et al. [30] provides a practical framework for assessing the validity, impact and applicability of SRs. For researchers and policy-makers aside from AMSTAR, the recently introduced ROBIS tool allows to comprehensively evaluate possible risk of bias in SRs at the review level.[34] At present it covers SRs with interventional, diagnostic, prognostic, and etiologic review questions and involves a three domain appraisal of the relevance of the respective review, an evaluation of possible risks of bias during the review process, and a concluding judgment of overall risk of bias of the review findings.[34]

Conclusion

Cancer-related SRs that are published in the CDSR demonstrate higher adherence to methodological and reporting standards than cancer-related SRs published in high-impact medical journals but are cited less frequently. Our assessment underscores the importance of performing a critical appraisal of SRs before including their evidence into guideline development or making individual clinical decisions.

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Ethical approval: Not required

Data sharing: No additional data available

Transparency: We affirm that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned have been explained.

Figure legends

Figure 1. PRISMA flow diagram of Cochrane reviews

Figure 2. PRISMA flow diagram of high-impact journal SRs

Figure 3. Forrest plot comparing to what extent Cochrane reviews and SRs published in high-impact journals meet criteria for methodological quality

Figure 4. Distribution of Cochrane reviews and high-impact journal SRs by review question

Figure 5. Distribution of Cochrane reviews and high-impact journal SRs by disease

Figure 6. Distribution of Cochrane reviews and high-impact journal SRs by intervention

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Table 1: Baseline characteristics of the included Cochrane reviews and high-impact journal SRs

	Cochrane	High-impact journals								
	Cochrane reviews (n=346)	*Total high-impact journal SRs (n=215)*	J Natl Cancer Inst (n=56)	J Clin Oncol (n=56)	Lancet Oncology (n=53)	The BMJ (n=22)	Lancet (n=14)	JAMA (n=12)	CA Cancer J Clin (n=1)	Cancer Research (n=1)
Year first published (Number of SR (%))										
2011	45 (13.1)	45 (20.9)	9 (16.1)	14 (25)	13 (24.5)	2 (9.1)	4 (28.6)	3 (25)		
2012	60 (17.3)	50 (23.2)	20 (35.7)	11 (19.6)	11 (20.8)	4 (18.2)	1 (7.1)	3 (25)		
2013	80 (23.1)	31 (14.4)	7 (12.5)	8 (14.3)	8 (15.1)	5 (22.7)	2 (14.3)	1 (8.3)		
2014	59 (17.1)	51 (23.7)	11 (19.6)	10 (17.9)	15 (28.3)	7 (31.8)	4 (28.6)	4 (33.3)		
2015	69 (19.9)	32 (14.9)	6) (10.7)	11 (19.6)	5 (9.4)	4 (18.2)	3 (21.4)	1 (8.3)	1 (100)	1 (100)
2016	33 (9.5)	6 (2.8)	3 (5.4)	2 (3.6)	1 (1.9)					
Region (Number of SR (%))										
Europe	233 (67.3)	95 (44.2)	14 (25)	20 (35.7)	34 (64.2)	12 (54.5)	13 (92.9)	1 (8.3)	1 (100)	
North America	26 (7.5)	88 (40.9)	33 (58.9)	27 (48.2)	10 (18.9)	6 (27.3)	1 (7.1)	10 (83.3)		1 (100)
Asia	49 (14.2)	16 (7.4)	6 (10.7)	3 (5.4)	3 (5.7)	3 (13.6)		1 (8.3)		
Australia/ New Zealand	19 (5.5)	14 (6.5)	2 (3.6)	6 (10.7)	6 (11.3)					
South America	13 (3.8)	1 (0.5)	1 (1.8)							
Africa	6 (1.7)	1 (0.5)				1 (4.5)				
Review type (Number of SR (%))										
Study-level	331 (95.7)	147 (68.4)	39 (69.6)	40 (71.4)	35 (66)	19 (86.4)	1 (7.1)	11 (91.7)	1 (100)	1 (100)

	Cochrane	High-impact journals								
	Cochrane reviews (n=346)	***Total high-impact journal SRs (n=215)***	J Natl Cancer Inst (n=56)	J Clin Oncol (n=56)	Lancet Oncology (n=53)	The BMJ (n=22)	Lancet (n=14)	JAMA (n=12)	CA Cancer J Clin (n=1)	Cancer Research (n=1)
data										
IPD	3 (0.9)	67 (31.2)	17 (30.4)	15 (26.8)	18 (34)	3 (13.6)	13 (92.9)	1 (8.3)		
Both	12 (3.5)	1 (0.5)		1 (1.8)						
Network Meta-Analysis (Number of SR (%))	2 (0.6)	6 (2.8)	3 (5.4)		3 (5.7)					
Study type (Number of SR (%))										
RCT	264 (76.3)	75 (34.9)	15 (26.8)	21 (37.5)	14 (26.4)	7 (31.8)	12 (85.7)	5 (41.7)	1 (100)	
non-RCT	5 (1.4)	85 (39.5)	27 (48.2)	16 (28.6)	27 (50.9)	12 (54.5)	1 (7.1)	2 (16.7)		
Both	77 (22.3)	46 (21.4)	9 (16.1)	19 (33.9)	9 (17)	3 (13.6)	1 (7.1)	5 (41.7)		
Unclear		9 (4.2)	5 (8.9)		3 (5.7)					1 (100)
Population (Number of SR (%))										
Adult	318 (9.9)	151 (70.2)	39 (69.6)	43 (76.8)	32 (60.4)	14 (63.6)	13 (92.9)	9 (75)	1 (100)	
Paediatric	26 (7.5)	6 (2.8)	1 (1.8)	1 (1.8)	4 (7.5)					
Both	2 (0.6)	22 (10.2)	5 (8.9)	6 (10.7)	7 (13.2)	4 (18.2)				
Unclear		36 (16.7)	11 (19.6)	6 (10.7)	10 (18.9)	4 (18.2)	1 (7.1)	3 (25)		1 (100)
Included studies (Median (IQR))	6 (2-13)	18 (10-38,8)	20 (12-43.8)	16 (9-36.3)	24 (12.8-44.8)	16 (9.6-26.5)	16 (25-9.8)	16.5 (10.3-24.8)	14	37

	Cochrane		High-impact journals							
	Cochrane reviews (n=346)	***Total high-impact journal SRs (n=215)***	J Natl Cancer Inst (n=56)	J Clin Oncol (n=56)	Lancet Oncology (n=53)	The BMJ (n=22)	Lancet (n=14)	JAMA (n=12)	CA Cancer J Clin (n=1)	Cancer Research (n=1)
Included patients (Median (IQR))	1020 (194.5-2845)	7730 (3288-29423)	8216 (3288-35568)	4758,5 (184.5-11091.8)	4600 (3033-21137)	117597 (10903-890992.3)	21471.5 (13287.5-45195.8)	12813.5 (4075.5-48067.3)	3377	Not reported
Citations (Median (IQR))	3 (1-7)	46 (18,5-86,5)	30.5 (9.8-55.3)	48,5 (18-70.3)	40 (22-97)	40 (15-80.3)	157 (54-351.8)	101 (45.3-155.8)	8	15

SR= systematic review, IPD= Individual Patient Data, J Natl Cancer Inst= Journal of the National Cancer Institute, J Clin Oncol= Journal of Clinical Oncology, CA Cancer J Clin= A Cancer Journal for Clinicians, Cancer Res= Cancer Research, RCT=randomised controlled trial, IQR= interquartile range

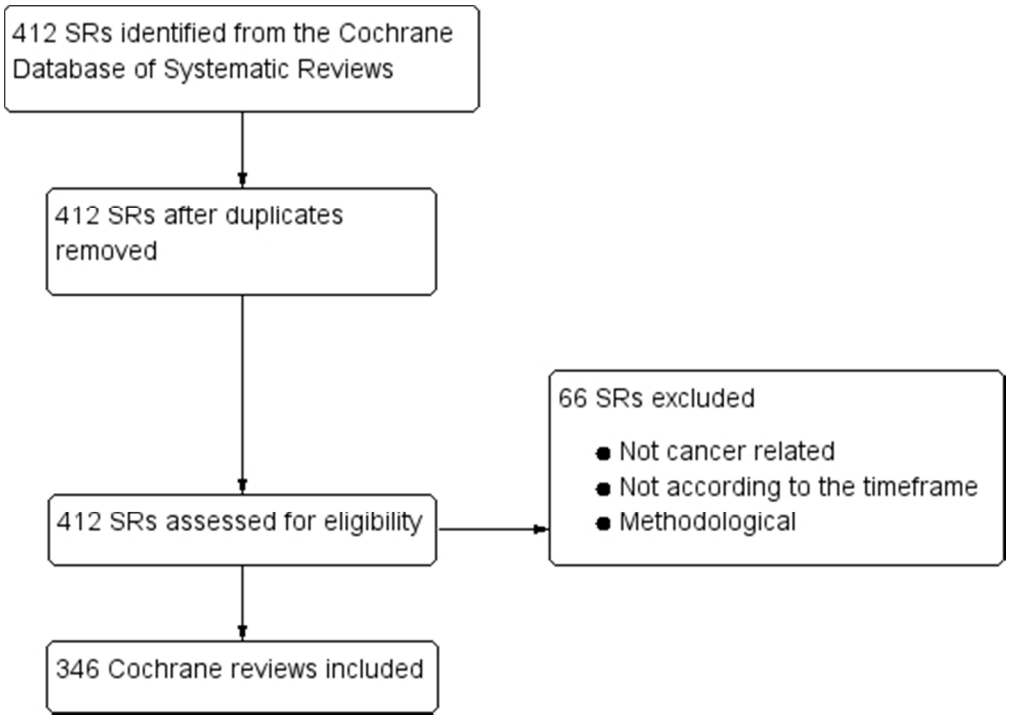

Figure 1. PRISMA flow diagram of Cochrane reviews

45x32mm (300 x 300 DPI)

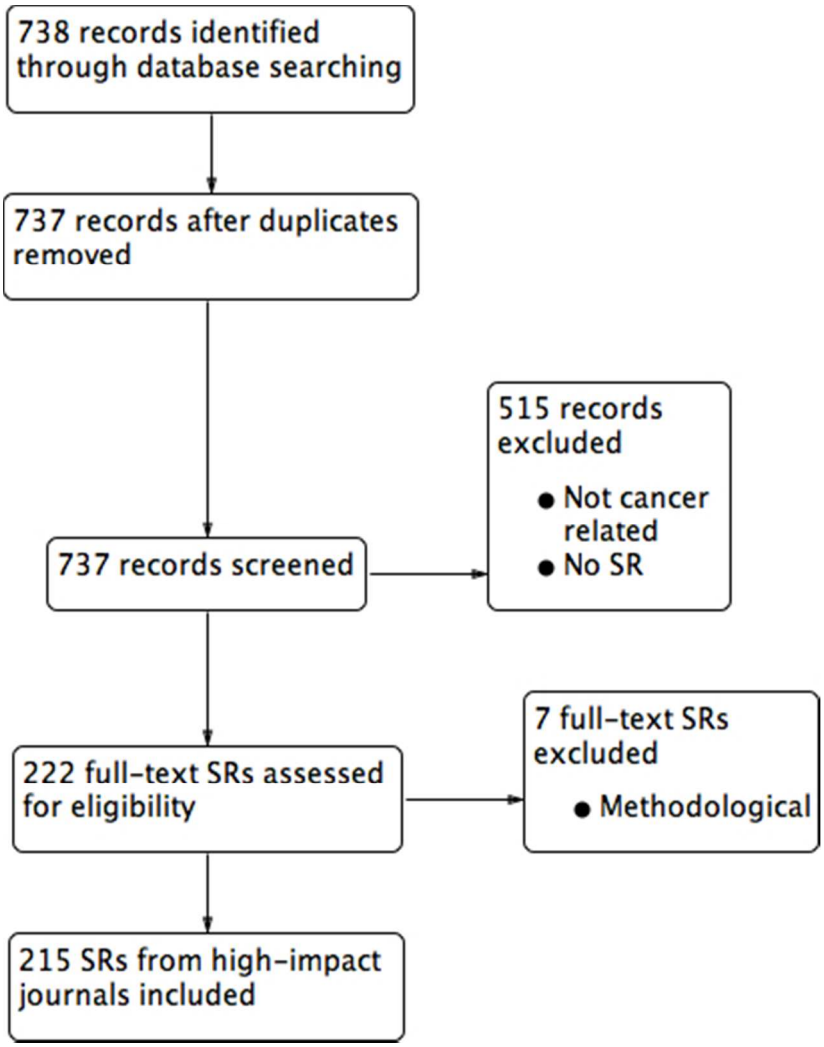

Figure 2. PRISMA flow diagram of high-impact journal SRs

34x43mm (300 x 300 DPI)

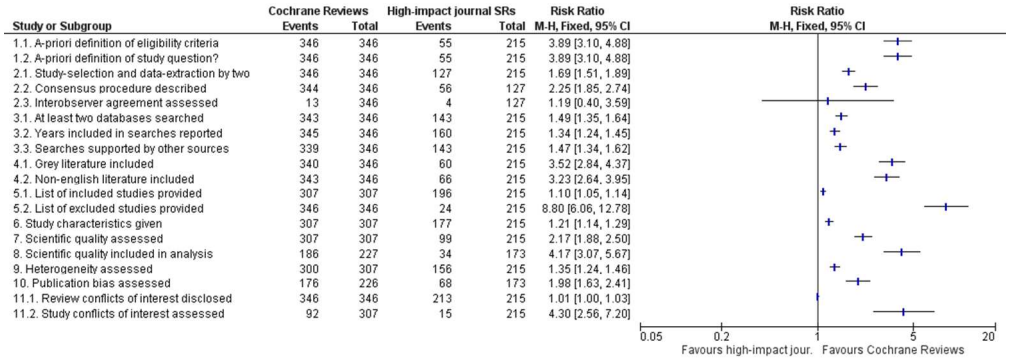

Figure 3. Forrest plot comparing to what extent Cochrane reviews and SRs published in high-impact journals meet criteria for methodological quality

89x32mm (300 x 300 DPI)

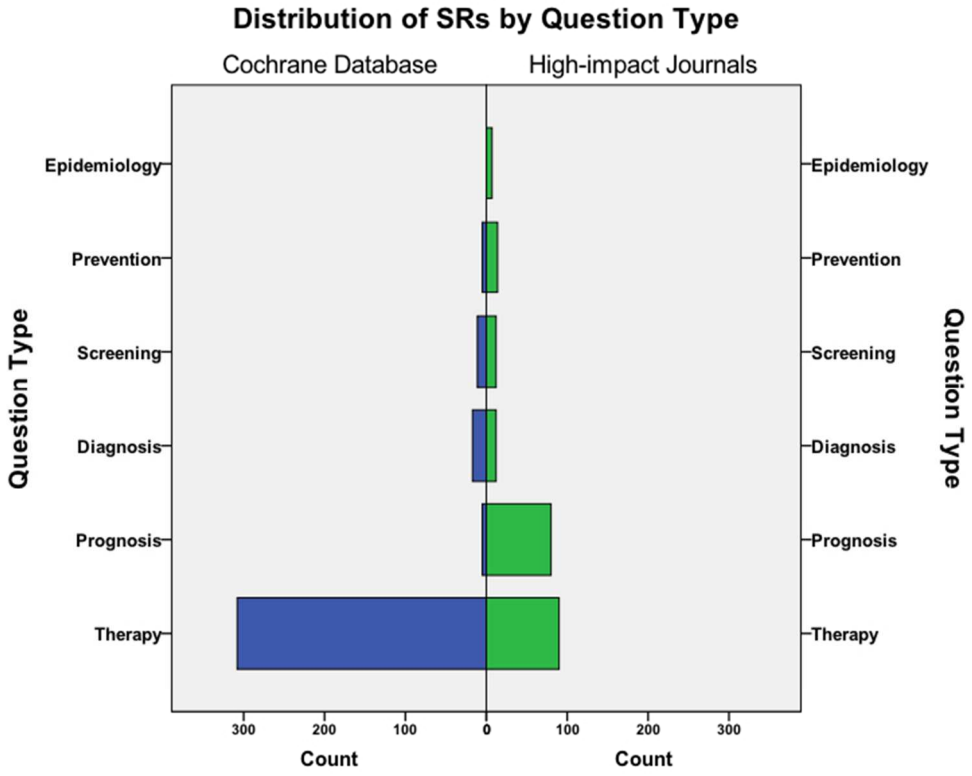

Figure 4. Distribution of Cochrane reviews and high-impact journal SRs by review question

63x50mm (300 x 300 DPI)

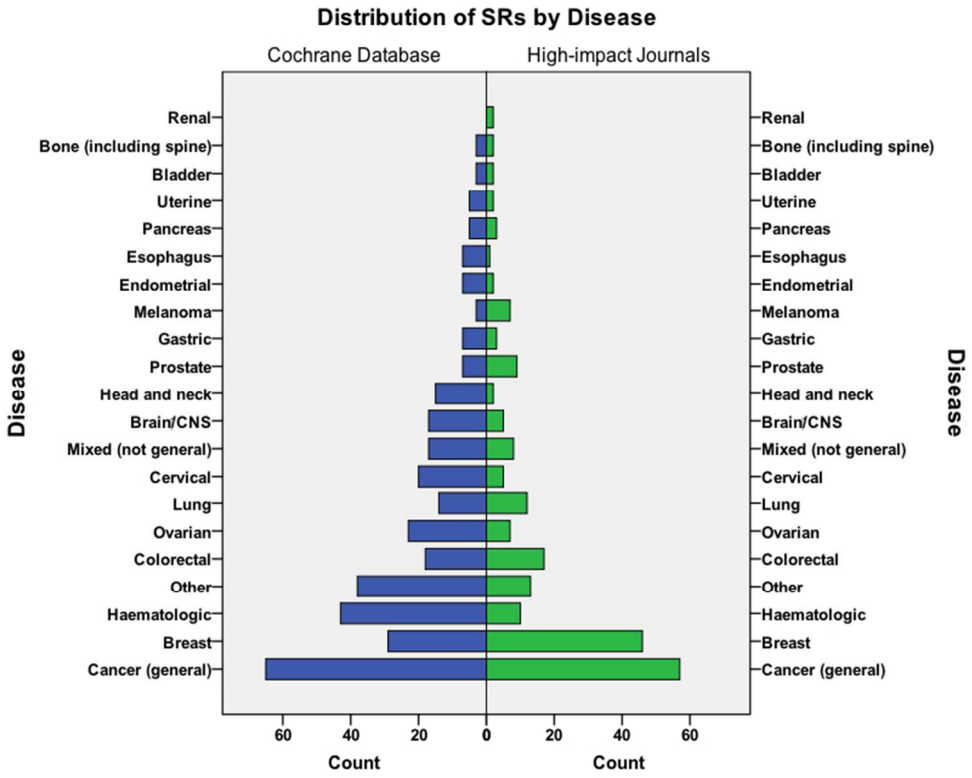

Figure 5. Distribution of Cochrane reviews and high-impact journal SRs by disease

69x55mm (300 x 300 DPI)

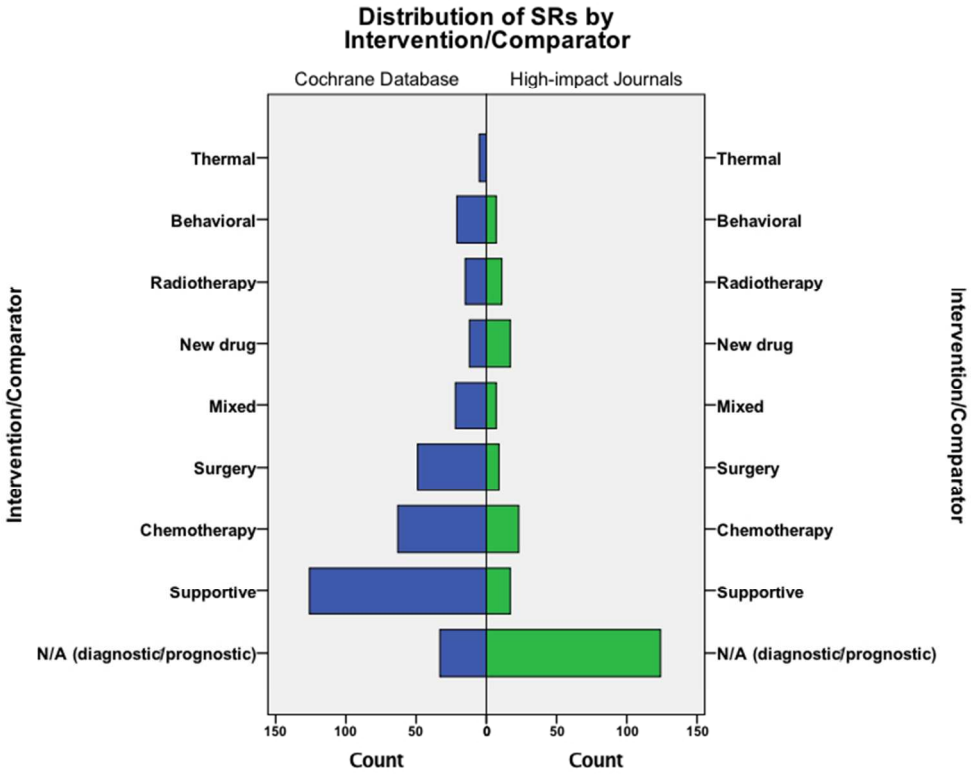

Figure 6. Distribution of Cochrane reviews and high-impact journal SRs by intervention

66x53mm (300 x 300 DPI)

Appendix

Appendix table 1: Search strategy for high-impact journals SRs

Search	
#1	Search ((((((((((((("Cancer Research"[Journal]) OR "Ca-A Cancer Journal for Clinicians"[Journal]) OR "Nature reviews. Clinical oncology"[Journal]) OR "Clinical cancer research : an official journal of the American Association for Cancer Research"[Journal]) OR)) OR ((((("BMJ (Clinical research ed.)"[Journal]) OR "The Lancet. Oncology"[Journal]) OR "JAMA"[Journal]) OR "The New England journal of medicine"[Journal]) OR "Journal of clinical oncology : official journal of the American Society of Clinical Oncology"[Journal]) OR "Annals of oncology : official journal of the European Society for Medical Oncology / ESMO"[Journal]) OR "Journal of the National Cancer Institute"[Journal]) OR "Lancet (London, England)"[Journal]))))))))))))
#2	Search ((((((((((((((((((((((((((((NEOPLASMS BY HISTOLOGIC TYPE[MeSH Terms]) OR NEOPLASMS BY SITE[MeSH Terms]) OR neoplas*) OR tumor*) OR tumour*) OR ((Krebs* or cancer*))) OR malignan*) OR ((carcino* or karzino* or karzinom*))) OR sarcom*) OR (leukem* or leukaem*)) OR lymphom*) OR melano*) OR metastas*) OR ((mesothelio* or mesotelio*))) OR carcinomatos*) OR ((gliom* or glioblastom*))) OR osteo*sarcom*) OR ((blastom* or neuroblastom*))))))))))))))
#3	Search (((((systematic review[Title/Abstract]) OR (((((meta-analys*[Title/Abstract]) OR metaanalys*[Title/Abstract]))))))))
#4	Search ((#1 and #2 and #3))
#5	Search (#1 and #2) Filters: Meta-Analysis; Systematic Reviews

#6	Search (#4 or #7) Filters: Publication date from 2011/01/01 to 2016/05/31

Appendix table 2: Extracted items

Item	Extracted	Example
1.	Author	
2.	Title	
3.	Journal	Cochrane, A Cancer Journal for Clinicians, New England Journal of Medicine, The Lancet, JAMA, Lancet Oncology, Journal of Clinical Oncology, The BMJ, Nature Reviews Clinical Oncology, Journal of the National Cancer Institute, Cancer Research
4.	Year last updated	2011-2016
5.	Year first published	2011-2016
6.	Cochrane group	
7.	Region of corresponding author	Africa, Asia, Australia/ New Zealand, Europe, North America, South America
8.	Review type	SR based on trial-level data, Individual Patient Data SR, Both
9.	Network Meta-Analysis	Yes, No
10.	Included study type	RCTs, non-RCTs, Both
11.	Question type	Diagnosis, Epidemiology, Prevention,

Item	Extracted	Example
		Prognosis, Screening, Therapy
12.	Disease	Bladder, bones (incl. spine), brain (incl. CNS), breast, cancer in general, cervical, colorectal, endometrial, oesophagus, gastric, haematological (leukaemia, lymphoma, myeloma), head and neck, lung, melanoma, mixed (but not general, other (e.g. male breast cancer, liver metastases), ovarian, pancreas, prostate, renal, uterus
13.	Intervention	Behavioural (e.g. exercise, diet, smoking), chemotherapy, mixed interventions, "new drug" (targeted therapy and monoclonal antibodies), radiotherapy, supportive, surgery, thermal (e.g. hyperthermia, crytotherapy), not applicable (if diagnostic, prognostic, preventive, epidemiologic, screening)
14.	Population	Adult, paediatric, both
15.	Number of included studies	
16.	Number included patients	

Appendix table 3: Extracted quality indicators

Item	AMSTAR	This work
1.	Was an 'a priori' design provided	Was the review question established before the conduct of the review?
		Were the in- and exclusion criteria defined before the conduct of the review?
2.	Was there duplicate study selection and data extraction?	Was the study selection and data-extraction undertaken by two independently working authors?
		Was the consensus procedure described?
		Was the interobserver-agreement (quantitatively) assessed?
3.	Was a comprehensive literature search performed?	Were at least two electronic databases searched?
		Were the years included in the searches reported?
		Were the database searches supported by other sources?
4.	Was the status of publication (i.e. grey literature) used as an inclusion criterion?	Were reviews irrespective of publication status included?
		Were reviews in languages other than English

Item	AMSTAR	This work
		included?
5.	Was a list of studies (included and excluded) provided?	Was a list of included studies provided?
		Was a list of excluded studies provided?
6.	Were the characteristics of the included studies provided?	Were study characteristic of every included study included?
7.	Was the scientific quality of the included studies assessed and documented?	Was the quality of included studies included by available tools (e.g. Cochrane's Risk of Bias, ROBINS, Newcastle-Ottawa scale)
8.	Was the scientific quality of the included studies used appropriately in formulating conclusions?	If a Meta-analysis was performed: Was the study quality included into the analysis via sensitivity- or subgroup analysis?
9.	Were the methods used to combine the findings of studies appropriate?	Was possible heterogeneity assessed?
10.	Was the likelihood of publication bias assessed?	Was possible publication bias formally assessed?
11.	Was the conflict of interest included?	Were possible Conflicts of Interest regarding the review disclosed?

Item	AMSTAR	This work
		Were possible Conflicts of Interest of the included studies reported?

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PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	2-3
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	4
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	4
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	5
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	5
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	6
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	6 and Appendix
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	6
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	7
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	7
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	7-8
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	8
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	8

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	NA
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	NA
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	9 and flow diagrams
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	NA
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	NA
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	9-12 and forest plot
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	NA
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	NA
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	NA
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	13-16
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	13-14
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	15-16
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	18

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097

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