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The correlation between heart failure and the risk of ischemic colitis: a systematic review and meta-analysis

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Abstract

Background Ischemic colitis is a relatively common gastrointestinal disease caused by hypoperfusion of the colon. Recently, studies have suggested an association between heart failure (HF) and ischemic colitis, even though the magnitude of the reported association varied considerably across the studies. This systematic review and meta-analysis were performed to comprehensively explore whether patients with HF are at a higher risk of ischemic colitis compared with individuals without HF by combining the results of all available observational studies.

Methods Systematic literature review was performed using EMBASE, MEDLINE and Google Scholar database up to May 2020. Eligible studies could be any observational ones that evaluated whether patients with HF have a higher risk of ischemic colitis than individuals without HF. Point estimates and standard errors from each eligible study were combined together using the generic inverse variance method of DerSimonian and Laird.

Results The systematic review identified 7 case-control studies and 1 cross-sectional study. The pooled analysis found that patients with HF had a significantly higher risk of ischemic colitis with the pooled odds ratio of 3.42 (95% confidence interval 1.49-7.82; I^2 96%). Funnel plot was relatively symmetric and was not suggestive of presence of publication bias.

Conclusion A significantly increased risk of ischemic colitis among patients with HF was demonstrated in this systematic review and meta-analysis.

Keywords Heart failure, ischemic colitis, epidemiology, meta-analysis, systematic review

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Introduction

Heart failure (HF) is a syndrome caused by cardiac abnormalities and neurohormonal changes, leading to elevated intracardiac pressures or reduced cardiac output [1]. The estimated incidence rate is approximately 300-400 new cases per 100,000 person-years, causing substantial healthcare and economic burden [2-5]. Symptoms and signs of HF include dyspnea, orthopnea, fatigue, peripheral edema, raised jugular venous pressure, cardiomegaly, and a third heart sound [6]. Common etiologies of HF are myocardial infarction, hypertension, valvular heart disease and cardiomyopathy [6].

With an incidence ranging from 4.5-45 new cases per 100,000 person-years [7,8], ischemic colitis is a relatively common gastrointestinal disease caused by hypoperfusion to the colon, leading to inflammation and hemorrhage of intestinal mucosa [9]. Classical clinical presentation of ischemic colitis is hematochezia and lower abdominal pain in patients aged older than 60 years [10]. Any conditions that can impair colonic perfusion, such as arterial emboli, thrombosis, trauma, hypotension and shock can predispose patients to ischemic colitis [10].

Recently, studies have suggested a relationship between HF and ischemic colitis, even though the magnitude of the reported association varied considerably [8,11-17]. Therefore, this systematic review and meta-analysis was performed to comprehensively explore whether patients with HF are at a higher risk of ischemic colitis compared with individuals without HF by combining the results of all available observational studies.

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Conflict of Interest: None

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Materials and methods

Information sources and search strategy

Two authors (W.W. and N.C.) independently conducted systematic literature review with no language limitation in EMBASE and MEDLINE database from inception to May 2020 to identify all published articles that explored the association between HF and ischemic colitis. The search strategy that includes the terms for "heart failure" and "ischemic colitis" is available as Supplementary Data 1. To maximize the comprehensiveness of the identification of eligible studies, the literature review was also performed in Google Scholar and bibliography of the included studies initially retrieved from EMBASE and MEDLINE. This study was performed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement (Supplementary Data 2).

Selection criteria

Eligible studies could be any observational ones that evaluated whether patients with HF have a higher risk of ischemic colitis than individuals without HF. Eligible cohort studies had to provide relative risks, incidence rate ratios, hazard risk ratios, or standardized incidence ratios with associated 95% confidence interval (CI) comparing the incidence of ischemic colitis between the 2 cohorts. Eligible case-control studies had to report odds ratios (OR) with 95%CI comparing the prevalence of HF between cases and controls. Eligible cross-sectional studies had to report OR with 95%CI of the association.

Data extraction

Standardized data collection form was used to extract the following details: last name of the first author; country of study; study design; year of publication; number of participants; recruitment of participants; identification and ascertainment of the diagnosis of HF and ischemic colitis; mean age of participants; percentage of male participants; confounders adjusted in multivariate analysis; and adjusted effect estimates with corresponding 95%CI. Two authors (W.W. and N.C.) assessed the quality of each cohort study according to Newcastle-Ottawa quality assessment scale [18].

Statistical analysis

Review Manager 5.3 software from the Cochrane Collaboration (London, United Kingdom) was used for all statistical analyses. To pool point estimates of all eligible studies together, the generic inverse variance method of DerSimonian and Laird was utilized in which the weight of each study for the pooled analysis was in reversal to its standard error [19]. Random-effect model, rather than fixed-effect model, was utilized as the eligible studies had different background populations and protocols. Cochran's Q test was utilized to determine statistical heterogeneity, further complemented by I^2 statistic which quantified the proportion of the total variation across studies incurring from heterogeneity rather than coincidence. A value of I^2 of 0-25% represented insignificant heterogeneity; 26-50% low heterogeneity; 51-75% moderate heterogeneity; and >75% high heterogeneity [20]. Visualization of funnel plot was used to evaluate for the presence of publication bias.

Results

A total of 1,336 articles (1,246 from EMBASE and 90 from MEDLINE) were identified. Duplication of 78 articles were removed, leaving 1,258 articles for title and abstract review. After the first round of title and abstract review, 1,210 articles were excluded as they obviously did not meet the eligibility criteria based on study design and type of article. As a result, 48 articles underwent further full-text review in which 42 articles were excluded because they did not investigate the association of interest, leaving 6 eligible studies for the meta-analysis. Review of bibliography of those eligible studies yielded 1 additional eligible study. Also, 1 additional eligible study was retrieved from Google Scholar. Finally, 7 case-control studies and 1 cross-sectional study were considered eligible and were included into the meta-analysis. Literature review and study selection process are summarized in Fig. 1. Description of study design, characteristics of participants and Newcastle-Ottawa assessment scales of the included studies are presented in Table 1.

Risk of ischemic colitis among patients with HF

As shown in Fig. 2, the pooled analysis found that patients with HF had a statistically significantly higher risk of developing ischemic colitis than individuals without HF with the pooled OR of 3.42 (95%CI 1.49-7.82). The statistical heterogeneity was high with an I^2 of 96%. The funnel plot of this meta-analysis was relatively symmetric and did not suggest the presence of publication bias (Fig. 3).

Discussion

This study is the first systematic review and meta-analysis to explore the risk of ischemic colitis among patients with HF. The pooled analysis found an approximately 3.4-fold increased risk of ischemic colitis. Concerning the potential mechanisms of this association, it is possible that ischemic colitis is a direct injury from reduced peripheral blood flow from low cardiac output in HF, as hypoperfusion to the colon is the principal pathogenesis of ischemic colitis [9]. In the state of reduced cardiac output in HF, blood flow is preserved for vital organs such as brain and heart by increased sympathetic activation and splanchnic vasoconstriction, resulting in reduced peripheral blood flow to tissue in gastrointestinal systems including the colon [21,22].

Table 1 Main characteristics of the studies included in the meta-analysis

Characteristics	Acosta [11]	Chang [12]	Fernandez [14]
Country	Sweden	United States	Spain
Study design	Case-control	Case-control	Case-control
Year of publication	2006	2008	2010
Total number of participants	Cases: 53 Controls: 212	Cases: 1,754 Controls: 6,970	Cases: 161 Controls: 322
Recruitment of participants	Cases: Cases were patients who died from fatal colonic infarction between 1970 and 1982 in Malmo, Sweden. Cases were identified from autopsy database of the city. Patients with acute occlusion of the SMA, NOMI, or mesenteric venous thrombosis were excluded Controls: Controls were patients without fatal colonic ischemia who were matched for sex, age at death and year of death to cases. They were identified from the same autopsy database	Cases: Cases with ischemic colitis were identified from the HealthCore Managed Care Database, which is an insurance claims database covering approximately 12 million members, between January 2000 and May 2005 Patients with intestinal infections caused by other organisms, infectious colitis, enteritis, and gastroenteritis or colitis, enteritis and gastroenteritis of presumed infectious origin within 14 days of the index date or patients who underwent enterectomy within 14 days after the index date or total colectomy within 14 days before the index date were excluded Controls: Controls without ischemic colitis were randomly identified from the same database. They were 1:4 matched to cases by age, sex, length of time in cohort and health plan/ geographic location	Cases: Cases were patients admitted to the Ourense Hospital Complex (Galicia, Spain) during the period January 1998 through March 2003 with diagnosis of ischemic colitis. They were identified from medical record database of the hospital. Controls: Controls were patients without ischemic colitis who were admitted to the Ourense Hospital Complex and underwent a colonoscopy during the same time period. They were also identified from medical record database of the hospital Patients with a diagnosis of colitis of any other origin (infectious, inflammatory, diverticulitis, associated with antibiotics or NSAIDs) were excluded from both groups
Diagnosis of HF	From autopsy	Presence of diagnostic code of HF in the database	Presence of diagnosis of HF made by physician in medical records
Diagnosis of ischemic colitis	From autopsy showing transmural colonic infarction and absence of small-bowel infarction or an infarction confined to the right colon and a patent SMA	Presence of ICD-9 CM codes for vascular insufficiency of intestine (557) and either a colonoscopy (45378–45387) or a partial colectomy (44140–44160) in the database	From endoscopic findings and compatible histopathology
Average age of participants (years)	N/A	Cases: 63.0 Controls: 63.0	Cases: 75.4 Controls: 75.8
Percentage of male	Cases: 49.1% Controls: 49.1%	Cases: 36.0% Controls: 36.0%	Cases: 44.1% Controls: 44.1%
Variables adjusted in multivariate analysis	None	None	Diabetes, dyslipidemia, peripheral arterial disease, digoxin, aspirin and other heart disease
Newcastle-Ottawa score	Selection: 3 Comparability: 1 Exposure: 3	Selection: 4 Comparability: 1 Exposure: 3	Selection: 4 Comparability: 2 Exposure: 3

(Contd...)

Table 1 *(Continued)*

Characteristics	Monkemuller [13]	Huerta [15]	Yadav [8]
Country	Germany	United Kingdom	United States
Study design	Case-control	Case-control	Case-control
Year of publication	2010	2011	2014
Total number of participants	Cases: 50 Controls: 50	Cases: 31 Controls: 2,000	Cases: 445 Controls: 890
Recruitment of participants	Cases: Cases with ischemic colitis were prospectively recruited during a 24-months period from the study hospital Controls: Controls without ischemic colitis were 1:1 matched to cases by age and sex	Cases: Cases with newly-diagnosed ischemic colitis between January 1994 and December 2001were identified from the General Practice Research Database which collected medical information from general practices across the United Kingdom Controls: Controls without ischemic colitis were randomly identified from the same database	Cases: Cases with ischemic colitis were identified from the database of Rochester Epidemiology Project between January 1, 1976 and December 31, 2009. This database contain health information of nearly all residents of Olmsted County, Minnesota Controls: Controls without ischemic colitis were randomly selected from the same database. They were 1:2 matched to cases by age and sex
Diagnosis of HF	N/A	Presence of diagnostic code of HF in the database	Presence of diagnostic code of HF in the database, subsequently confirmed by medical record review
Diagnosis of ischemic colitis	Physician diagnosis using Brandt's criteria	Presence of diagnostic code of ischemic colitis in the database, subsequently confirmed by medical record review using Brandt's criteria	Presence of diagnostic code of ischemic colitis in the database, subsequently confirmed by medical record review
Average age of participants (years)	Cases: 71.0% Controls: 71.0%	N/A	Cases: 71.6% Controls: 71.6%
Percentage of male	Cases: 54.0% Controls: 54.0%	Cases: 48.4% Controls: 46.8%	Cases: 33.0% Controls: 33.0%
Variables adjusted in multivariate analysis	None	Age, sex, calendar year, body mass index, coagulation disease, cancer and number of visits to general practitioners	None
Newcastle-Ottawa score	Selection: 2 Comparability: 1 Exposure: 1	Selection: 4 Comparability: 2 Exposure: 3	Selection: 4 Comparability: 1 Exposure: 3
Characteristics	Uchida [16]	Twohig [17]	
Country	Japan	United States	
Study design	Case-control	Cross-sectional	
Year of publication	2018	2014	

(Contd...)

Table 1 *(Continued)*

Characteristics	Uchida [16]	Twohig [17]
Total number of participants	Cases: 209 Controls: 209	57,118,010 (1560 patients with ischemic colitis and 57116450 patients without ischemic colitis)
Recruitment of participants	Cases: Cases with ischemic colitis were identified from electronic records of colonoscopy performed in Tokai University Hospital between December 2004 and March 2017 Controls: Controls without ischemic colitis were selected from the same electronic records They were 1:1 matched to cases by sex and age	Participants were all patients in the United States in IBM Explorys database (1999-2018)
Diagnosis of HF	Presence of diagnosis of HF made by physician in medical records	Presence of diagnostic code of HF in the database
Diagnosis of ischemic colitis	Diagnosis of ischemic colitis based on comprehensive medical record review of clinical course, physical findings, blood data and colonoscopy findings	Presence of diagnostic code of ischemic colitis in the database
Average age of participants (years)	Cases: 64.9 Controls: 64.9	N/A
Percentage of male	Cases: 28.7% Controls: 28.7%	N/A
Variables adjusted in multivariate analysis	Smoking, alcohol, abdominal surgery, hypertension, diabetes, chronic kidney disease, chronic obstructive lung disease, stroke, cancer, irritable bowel syndrome, laxative, antiplatelet, anticoagulants and steroid	None
Newcastle-Ottawa score	Selection: 4 Comparability: 2 Exposure: 3	Selection: 5 Comparability: 0 Exposure: 3

HF, heart failure; HICDA-2, Hospital Adaptation of the International Classification of Disease, second edition; ICD-9, International Classification of Diseases, 9th revision; ICD-9-CM, International Classification of Diseases, 9th revision, Clinical Modification; ICM-10, International Classification of Diseases, 10th revision; LHIRD2005, Longitudinal Health Insurance Database 2005; the National Health Insurance Research Database; NOMI, non-occlusive mesenteric ischemia; N/A, not available; SMA, superior mesenteric artery; SNOMED, systematized nomenclature of medicine

The circulation to the gastrointestinal tract could be further jeopardized by acute exacerbation of HF by any precipitating factors, such as excessive salt intake, arrhythmias [23] or infection [24], causing acute insufficiency of blood supply in the colon.

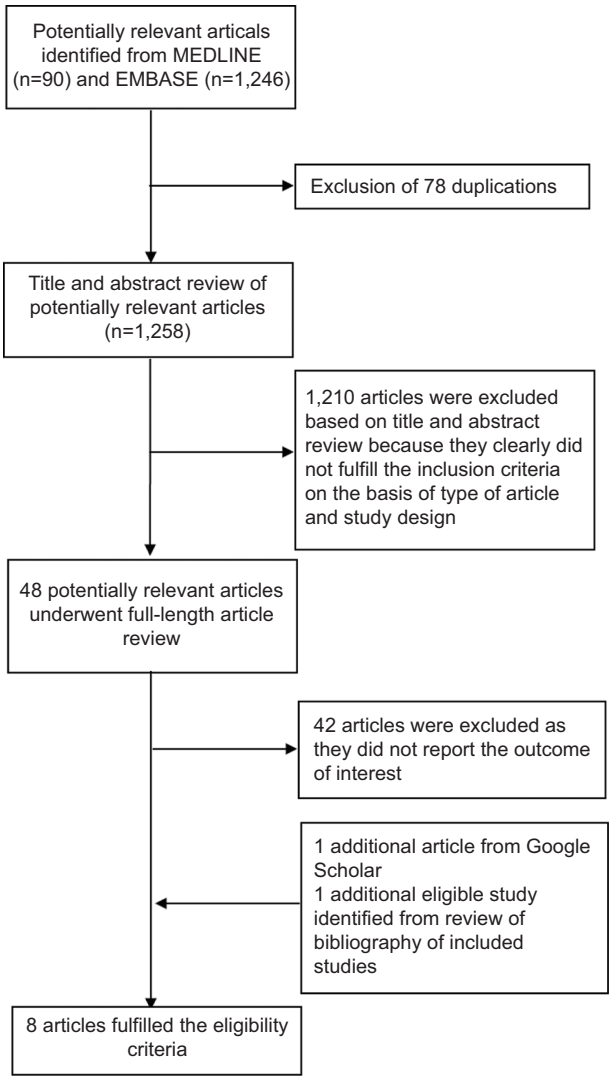

Figure 1 Literature review and study selection process

Another possible explanation is embolic phenomenon. It is well known that HF increases the risk of atrial fibrillation [25]. Increased intracardiac filling pressure, dysregulation of intracellular calcium of cardiac myocytes, and neurohormonal activation in HF contribute to atrial remodeling, fibrosis and development of atrial fibrillation [26]. Atrial fibrillation is a primary risk factor for systemic emboli [27]. Cardiac emboli to branches of inferior mesenteric artery can block blood supply to colon and cause ischemic colitis.

The increased risk may run through the shared atherosclerotic risk factors between the 2 conditions. The most common etiology of HF is coronary artery disease [28], a result of the narrowing of coronary artery by atherosclerotic plaque [29]. Therefore, risk factors of HF are similar to other atherosclerotic diseases, which include atherosclerotic occlusion of non-coronary vessels such as inferior mesenteric branches responsible for ischemic colitis [30].

This meta-analysis carries some limitations that should be recognized. First, the 5 studies [8,12,14,15,17] included in this meta-analysis relied on registry data and diagnostic codes to diagnose HF and ischemic colitis, potentially jeopardizing the diagnostic accuracy and completeness of case identification. Second, only 2 [14,16] of the 8 included studies adjusted their effect estimates for atherosclerotic risk factors (hypertension, dyslipidemia, diabetes mellitus, obesity, and smoking). Consequently, this association might be a result of those confounders rather than a true association. Also, only 2 studies [14,16] had a perfect Newcastle-Ottawa score while the rest had only fair quality with the score ranging from 4-8 points, which may have jeopardized the validity of the pooled effect estimates. Additionally, due to the limited geographical distribution of the studies (3 studies from the United States, 4 studies from Europe, 1 study from Asia, and none from Africa and South America), the results may not be generalizable to every population. Last, even though funnel plot of this study is symmetric, the interpretation of this plot is limited by the relatively small number of eligible studies. Therefore, publication bias in favor of studies that report positive association may have been present.

In conclusion, a significantly increased risk of ischemic colitis among patients with HF was observed in this systematic review and meta-analysis.

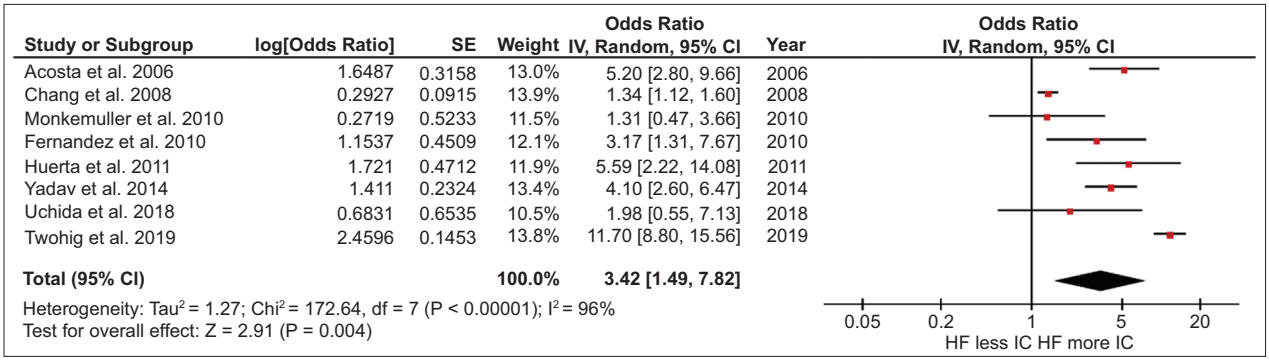

Figure 2 Forest plot of meta-analysis of the association between heart failure (HF) and ischemic colitis (IC)
CI, confidence interval; SE, standard error

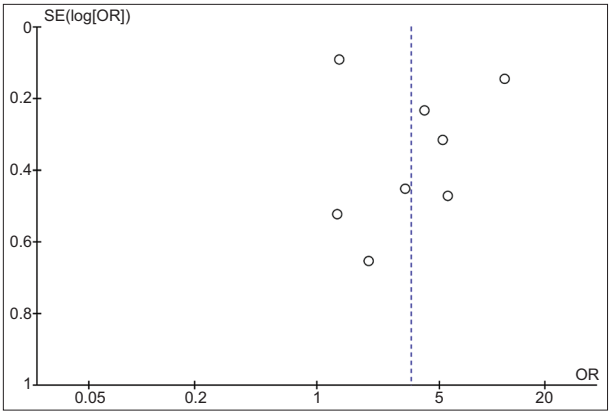

Figure 3 Funnel plot of meta-analysis of the association between heart failure and ischemic colitis
OR, odds ratio; SE, standard error

Summary Box

What is already known:

- Known risk factors of ischemic colitis include conditions that can impair colonic perfusion, such as arterial emboli, thrombosis, and hypotension

What the new findings are:

- The pooled analysis found that patients with heart failure had a significantly higher risk of developing ischemic colitis than individuals without heart failure
- Based on the pooled analysis of the 8 included studies, the risk was increased by approximately 3.4-fold
- Possible mechanisms were reduced colonic blood flow from low cardiac output and increased risk of embolic phenomenon

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Supplementary material

Supplementary Data 1 Search strategy

EMBASE

1. 'ischemic colitis'/exp OR 'ischemic colitis'
2. 'mesenteric ischemia'/exp OR 'mesenteric ischemia'
3. 'colitis'/exp OR 'colitis'
4. 'ischemia'/exp OR 'ischemia'
5. #3 AND #4
6. #1 OR #2 OR #5
7. 'heart failure' OR 'heart failure'/exp
8. 'congestive heart failure' OR 'congestive heart failure'/exp
9. 'CHF' OR 'CHF'/exp
10. 'diastolic heart failure' OR 'diastolic heart failure'/exp
11. 'systolic heart failure' OR 'systolic heart failure'/exp
12. 'systolic dysfunction'/exp OR 'left ventricular systolic dysfunction'/exp
13. #7 OR #8 OR #9 OR #10 OR #11 OR #12
14. #6 AND #13

MEDLINE

1. ischemic colitis.mp. or exp Ischemic Colitis/
2. mesenteric ischemia.mp. or exp Mesenteric Ischemia/
3. colitis.mp. or exp Colitis/
4. ischemia.mp. or exp Ischemia/
5. 3 and 4
6. 1 or 2 or 5
7. heart failure.mp. or exp Heart Failure/
8. diastolic heart failure.mp. or exp Heart Failure, Diastolic/
9. systolic heart failure.mp. or exp Heart Failure, Systolic/
10. CHF.mp.
11. 7 or 8 or 9 or 10
12. 6 and 11

Supplementary Data 2 Prisma

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.	1
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	3
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	3-4
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.	4 and Supplement data 1
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.	5
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	4 and Supplement data 1
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).	5
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.	5
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	5
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.	N/A
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	5
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.	6
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).	N/A
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	N/A

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.	6-7
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.	Table 1
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).	N/A
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.	Figure 2
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	7
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	N/A
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	N/A
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).	7-9
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).	9
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	10
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.	10

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group. Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. *PLoS Med* 2009;6:e1000097.