

Nonalcoholic Fatty Liver Disease and Urolithiasis. A Systematic Review and Meta-Analysis

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ABSTRACT

Background & Aims: Recent studies have suggested that nonalcoholic fatty liver disease (NAFLD) could be a predisposing factor for urolithiasis but the results have been inconsistent. This systematic review and meta-analysis was conducted with the aim to summarize all available data.

Methods: A comprehensive literature review was conducted using MEDLINE and EMBASE databases through March 2018 to identify all studies that compared the risk of urolithiasis among patients with NAFLD versus those without NAFLD. Effect estimates from each study were extracted and combined together using the random-effect, generic inverse variance method of DerSimonian and Laird.

Results: A total of eight studies with 238,400 participants fulfilled the eligibility criteria and were included in the meta-analysis. The risk of urolithiasis among patients with NAFLD was significantly higher than in those without NAFLD with a pooled odds ratio of 1.81 (95% confidence interval, 1.29-2.56; I^2 92%).

Conclusions: A significantly increased risk of urolithiasis among patients with NAFLD was observed in this meta-analysis.

Key words: Nonalcoholic fatty liver disease – nonalcoholic steatohepatitis – urolithiasis – kidney stone – meta-analysis.

Abbreviations: CT: computer tomography; NAFLD: nonalcoholic fatty liver disease.

INTRODUCTION

Nonalcoholic fatty liver disease (NAFLD) is a common disease characterized by fatty infiltration of the liver of greater than five percent of the liver weight that is not caused by other liver diseases or excessive alcohol consumption [1]. It has been estimated over 60 million people in the United States are affected by this disorder [2, 3]. The pathogenesis of NAFLD is closely linked to chronic systemic inflammation and insulin resistance [4]. There are several known risk factors for NAFLD such as obesity, diabetes mellitus, hypertension, hyperuricemia, chronic kidney disease, physical inactivity and hypothyroidism [4-6].

Urolithiasis is one of the most common urological diseases caused by deposition of crystals in the renal medulla and genitourinary tract. Studies have demonstrated that the prevalence of urolithiasis in the United States increased from 4% in the year 1976 to 1980 to 8% in the year 2007 to 2010 [7, 8]. Recent epidemiological studies have shown that urolithiasis is associated with several metabolic disorders, including obesity, diabetes mellitus and hypertension. Some authors even consider urolithiasis as a component of metabolic syndrome [9-12].

Recent studies have suggested that NAFLD could also be a risk factor for urolithiasis although the results varied considerably across the studies [9, 13-19]. The current systematic review and meta-analysis was conducted with the aims to identify all studies that compared the risk of urolithiasis among patients with NAFLD versus individuals without NAFLD and to summarize the results of those studies together.

METHODS

Information Sources and Search strategy

A systematic literature search of the MEDLINE and EMBASE databases was carried out from inception to March

2018 to identify all original studies that investigated the association between NAFLD and urolithiasis. The systematic literature review was independently conducted by three investigators (K.W., P.P., and P.U.) using a search strategy that included the terms for “nonalcoholic fatty liver disease”, “steatohepatitis”, “urolithiasis”, “kidney stone”, “ureteral stone”, and “bladder stone” as described in online Supplementary Table I. No language limitation was applied. Abstracts of several prominent conferences, including Digestive Disease Week from 2010 to 2018, American College of Gastroenterology from 2004 to 2018, American Association for the Study of Liver Diseases from 2003 to 2018, United European Gastroenterology from 2009 to 2018 and European Congress of Radiology from 2003 to 2018, were also searched. Hand-search was also performed on references of selected retrieved articles. The meta-analysis was conducted according to the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analysis) statement, which is provided as the online Supplementary Table II.

Selection criteria

To be eligible for the meta-analysis, studies had to be cross-sectional, case-controlled or cohort studies that investigated the risk of urolithiasis among patients with NAFLD versus individuals without NAFLD. For the cohort study and cross-sectional study, cases must be patients with NAFLD and comparators must be individuals without NAFLD. One of the reported outcomes must be urolithiasis (incident urolithiasis for cohort study and prevalent urolithiasis for cross-sectional study). For the case-control study, cases must be patients with urolithiasis and controls must be individuals without urolithiasis. The exposure of interest must be the history of NAFLD. Eligible studies must also provide the effect estimates [odds ratios (OR), relative risks (RR), hazard ratios (HR) or standardized incidence ratio (SIR)] with 95% confidence intervals (CI). Inclusion was not limited by study size. When more than one article utilizing the same database/cohort was available, only one study with the most comprehensive data/analyses was included.

Retrieved articles were reviewed for their eligibility independently by the same three investigators (K.W., P.P., and P.U.) with disagreements resolved by consensus. The Newcastle-Ottawa quality assessment scale was used to appraise the quality of the studies in three domains, including the recruitment of participants, the comparability between the groups as well as the ascertainment of the outcome of interest for the cohort study and the ascertainment of the exposure of interest for the case-control study [20]. The modified Newcastle-Ottawa scale, described by Herzog et al., was used for the cross-sectional study [21].

Data extraction

The investigators used a structured information collection form to extract the following data from each study: title of the study, name of the first author, publication year, year of the study, country where the study was conducted, number of subjects, demographics of subjects, methods used to identify and verify NAFLD and urolithiasis, adjusted effect estimates with 95% CI and covariates that were adjusted in the multivariable analysis.

To ensure accuracy, this data extraction process was independently performed by two investigators (K.W. and P.P.) and was reviewed by the senior investigator (P.U.).

Statistical analysis

Data analysis was performed using the Cochrane Collaboration's Review Manager 5.3 software (London, United Kingdom). Adjusted point estimates from each study were consolidated by the generic inverse variance method of DerSimonian and Laird, which assigned the weight of each study for the pooled analysis based on its variance [22]. As the outcome of interest was relatively uncommon, we planned to use the RR and HR of cohort studies as an estimate for the OR to calculate the pooled effect estimates with OR of case-control studies and cross-sectional studies. In light of the high probability of between-study variance because of different study designs, populations and methodologies, a random-effect model was used. Cochran's Q test and I² statistic were used to quantify the between-study heterogeneity. A value of I² of 0-25% represents insignificant heterogeneity, 26-50% represents low heterogeneity, 51-75% represents moderate heterogeneity, and more than 75% represents high heterogeneity [23]. Funnel plot was used for the assessment of the presence of publication bias.

RESULTS

A total of 347 potentially eligible articles were identified using the described search strategy (135 from Medline and 212 from EMBASE). After the exclusion of 128 duplicate articles, titles and abstracts of 219 unique articles were reviewed. One hundred and ninety-one articles were excluded at this stage since they were case reports, case series, correspondence, review articles, *in vitro* studies, animal studies or interventional studies, leaving 28 articles for full-text review: 18 of them were excluded after the full-length review, as they did not report the outcome of interest while 4 articles were excluded since they were descriptive studies without comparative analysis. Two conference abstracts were identified from searching of conference abstract databases. Finally 8 studies [9, 13-19] with 238,400 participants were included in the meta-analysis. The literature retrieval, review and selection process are shown in Fig. 1. The characteristics and quality appraisal of the included studies are presented in Table I. Inter-rater agreement for the quality assessment using the Newcastle-Ottawa scale was high with the kappa statistic of 0.80.

Association between nonalcoholic fatty liver disease and urolithiasis

We found a significantly increased risk of urolithiasis among patients with NAFLD with the pooled OR of 1.81 (95% CI, 1.29-2.56) as demonstrated in Fig. 2. The between-study heterogeneity was high with an I² of 92%.

Subgroup analysis

Subgroup analysis was conducted based on the methods used to diagnose urolithiasis (ultrasonography, computerized tomography [CT] and questionnaire) (Table I). The magnitude of the association was at the highest with the studies that used

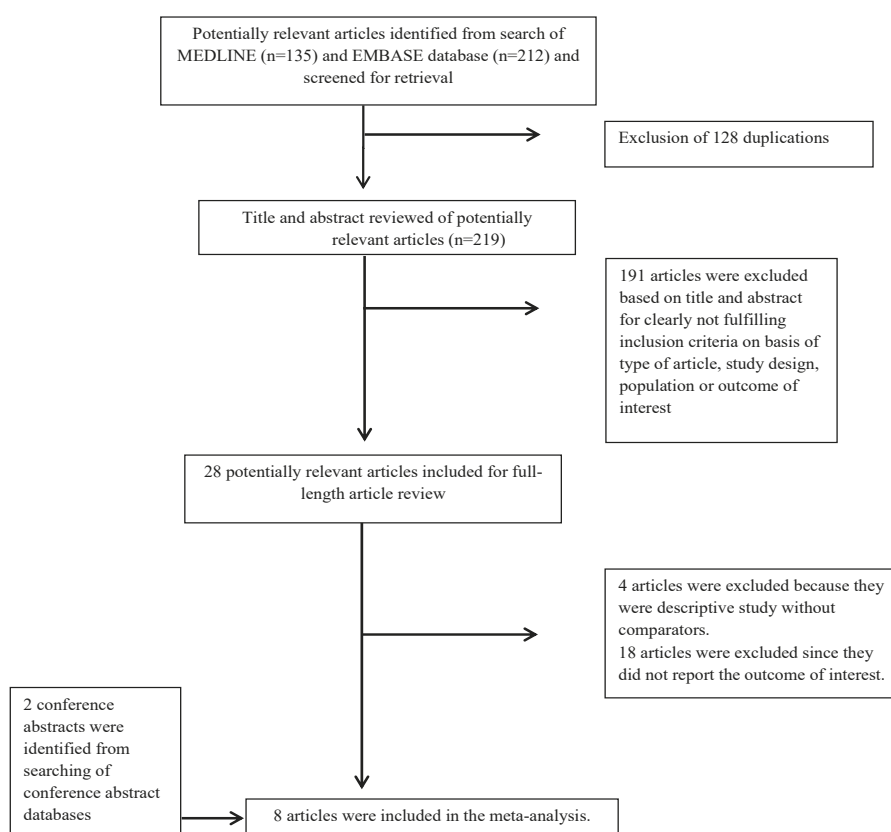


Fig. 1. Literature review process.

CT (pooled OR 2.83; 95% CI, 1.14 – 7.00; I² 90%), followed by ultrasonography (pooled OR 1.49; 95% CI, 0.79 – 2.78; I² 96%) and a questionnaire (pooled OR 1.29; 95% CI, 1.02 – 1.61).

Sensitivity analysis

To further explore the high heterogeneity of this meta-analysis, a sensitivity analysis was performed by excluding the studies that did not adjust their effect estimates for comorbidities (i.e., excluding studies that did not adjust their results at all and studies that adjusted their results for only age and sex). A total of four studies [14, 17–19] remained in this sensitivity analysis and the new pooled OR decreased slightly to 1.21 (remained statistically significant with 95% CI of 1.00 – 1.45). Between-study statistical heterogeneity decreased to low level with I² of 28%.

Evaluation for publication bias

A funnel plot was constructed based on the effect estimate and accuracy of each study to assess for the presence of publication bias (Fig. 3). The plot is relatively asymmetric and is suggestive of the presence of publication bias in favor of positive studies.

DISCUSSION

The current systematic review and meta-analysis of studies on the association between NAFLD and risk of urolithiasis found an almost two-fold increased risk of urolithiasis among patients with NAFLD compared with individuals without NAFLD. The mechanism behind the increased risk is not known with certainty but there are a few possible explanations.

First, several classic metabolic risk factors for NAFLD, such as obesity, hypertension, diabetes mellitus and metabolic syndrome, have been increasingly recognized as predisposing factors for urolithiasis as well [24]. Studies have suggested that insulin resistance, the cornerstone of metabolic syndrome, may contribute to impaired ammonia synthesis by the kidneys. Insulin receptors are expressed in the renal tubular epithelium and insulin plays a significant role in the ammoniogenesis [25, 26]. Therefore, insulin resistance would lead to a decrease in urinary ammonia synthesis and excretion, resulting in lower urinary pH [10, 25]. In addition, patients with NAFLD are also often found to have hyperuricemia [6]. These two factors would serve as fertile ground for the formation of uric acid stones, although we do not have data from the primary studies whether the magnitude of the increased risk was more pronounced with uric acid stones. Obesity and insulin resistance may also directly alter the urine composition and increase the likelihood of stone formation. For instance, a large study of almost 6,000 participants found a higher concentration of metabolites and waste known to be associated with the formation of stones in the urine of obese participants [27].

Another possible explanation involves the role of inflammation and reactive oxygen species. Studies have suggested that membrane-bound vesicles from cells that die from oxidative stress could serve as the nidus for stone formation [28]. The kidney is an especially vulnerable organ to oxidative injury due to the abundance of long-chain polyunsaturated fatty acids in renal lipids [15]. Patients with NAFLD and metabolic syndrome are known to have a higher inflammatory burden and, therefore, a higher likelihood of renal oxidative cell death [29, 30].

Table I. Main characteristics of the studies included in this meta-analysis

Study / Country / year	Einollahi et al [9] Iran / 2013	Paz et al [16] Israel / 2015	Nam et al [15] South Korea / 2016	Weiss et al [18] USA / 2017	Kim et al [14] DSouth Korea / 2017	Zeina et al [19] Israel / 2017	Wei et al [17] China / 2018	Arias et al [13] Colombia / 2018
Study design	Cross sectional study	Cross sectional study	Cross sectional study	Cross sectional study	Prospective cohort study	Cross sectional study	Cross sectional study	Cross sectional study
Participants	11,245 individuals who underwent ultrasonographic evaluation of the abdomen at Baqiyatallah-alazam Hospital, Iran	100 individuals who underwent stone-protocol CT scan due to renal colic at the study hospital	1,381 individuals who underwent CT scan evaluation of the abdomen and pelvis at Haeundae Paik Hospital, South Korea, in July 2015	11,859 individuals aged 20 to 74 years who underwent ultrasonographic evaluation of the liver as a part of NHANES III study from 1988 to 1994.	208,578 individuals aged 18 years and over who participated in the Kangbuk Samsung Health Study and underwent comprehensive examination as well as ultrasonographic evaluation of the abdomen at the Kangbuk Samsung Hospital Korea, from January 2002 to December 2014. Participants were required to have at least one follow-up visit after the initial examination.	508 individuals aged 18 years and over who underwent stone-protocol CT scan due to clinically suspected renal colic at the Hillel-Yaffe Medical Center Hospital from 2013 to 2014.	3,719 men aged 17 to 88 years who participated in routine physical examination at Medical Center, Fangchenggang First People's Hospital from September 2009 to December 2009. Ultrasonographic evaluation of the abdomen was a part of this routine examination.	1,010 individuals aged 18 years and over who underwent abdominal CT scan at the study hospital from July 2013 to July 2014.
Diagnosis of NAFLD	fatty liver on ultrasonography	fatty liver on CT scan (liver attenuation <10 HU compare to spleen or liver attenuation <40HU)	fatty liver on CT scan without any secondary causes	fatty liver on ultrasonography without any secondary causes	fatty liver on ultrasonography without any secondary causes	fatty liver on CT scan	fatty liver on ultrasonography without any secondary causes	fatty liver on CT scan (liver to spleen density ratio <0.8)
Diagnosis of nephrolithiasis	stones in the renal system on ultrasonography	stones in the renal system on CT scan	stones in the renal system on CT scan	Self-report via health questionnaire (as a part of NHANES III)	stones in the renal system on ultrasonography	stones in the renal system on CT scan	stones in the renal system on ultrasonography	Presence of stones in the renal system on CT scan
Confounder adjusted in multivariate analysis	None	None	Age and sex	Age, sex, race, BMI, GFR, smoking status, HTN, gout, DM and high liver enzymes	Age, center, year of screening, smoking status, alcohol intake, BMI, history of HTN and DM, HOMA-IR, uric acid and hsCRP	Age, sex, DM and visceral fat	Age, education status, smoking, alcohol consumption, physical activity and BMI	Age and sex
Quality assessment (Newcastle-Ottawa scale)	Selection: 3 Comparability: 1 Outcome: 3	Selection: 2 Comparability: 1 Outcome: 3	Selection: 3 Comparability: 1 Outcome: 3	Selection: 3 Comparability: 2 Outcome: 4	Selection: 3 Comparability: 2 Outcome: 4	Selection: 2 Comparability: 2 Outcome: 3	Selection: 2 Comparability: 2 Outcome: 3	Selection: 2 Comparability: 1 Outcome: 3

NAFLD; nonalcoholic fatty liver disease; CT; computed tomography; HU; Hounsfield unit; BMI; body mass index; HTN; hypertension; DM; diabetes mellitus; HOMA-IR; homeostatic model assessment for insulin resistance; hsCRP; high sensitivity C-reactive protein; NHANES; National Health and Nutritional Examination Survey; GFR; glomerular filtration rate

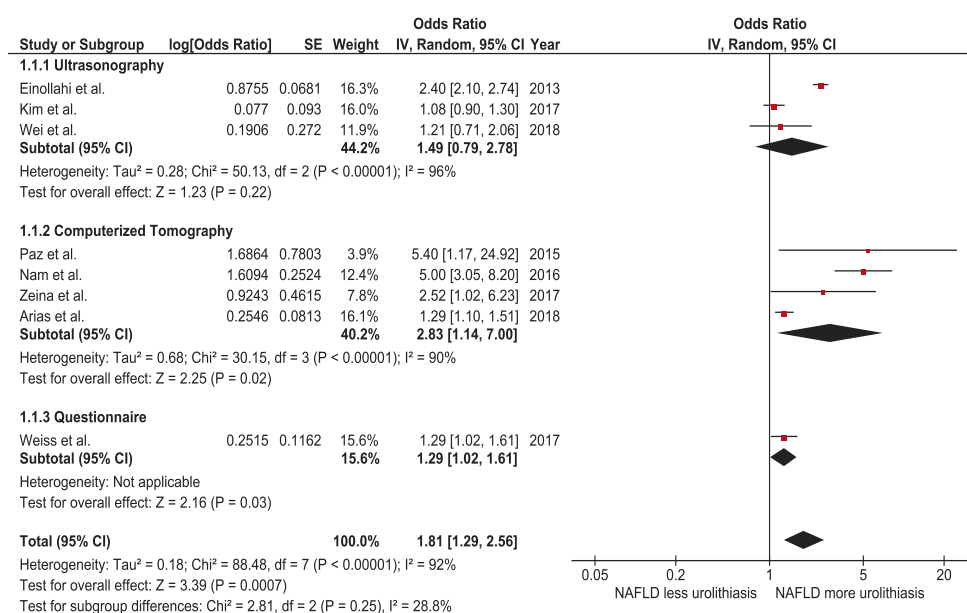


Fig. 2. Forest plot of all studies.

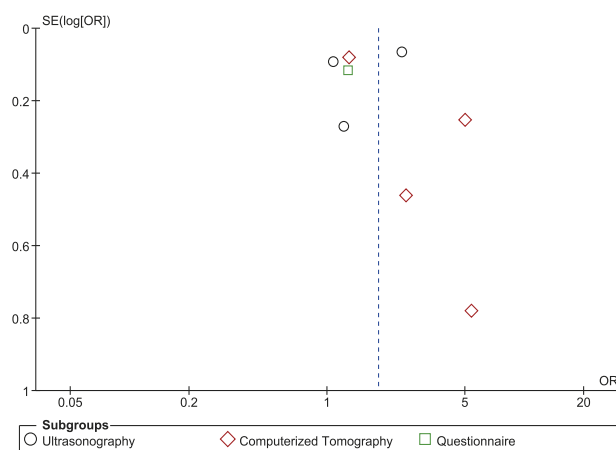


Fig. 3. Funnel plot of all studies.

Data on the association between the severity of NAFLD and the magnitude of the risk of urolithiasis are limited. Only one study investigated such a relationship. The authors divided NAFLD into mild, moderate and severe categories based on ultrasonographic appearance and found a significant correlation between the magnitude of the risk of urolithiasis and the severity of NAFLD (p for trend = 0.04) [17].

Although the included studies were of high quality as reflected by their high Newcastle-Ottawa scores, we acknowledge that this systematic review and meta-analysis has some limitations and the results should be interpreted with caution.

First, statistical heterogeneity was high in the meta-analysis. We believe that the variation of quality of the effect estimates from each study was responsible for this as the sensitivity analysis that included only studies with more reliable results (i.e., studies that appropriately adjusted their effect estimates for potential confounders) showed I^2 of only 28%. There was also an inconsistency in the methods/criteria used for the diagnosis of NAFLD. Secondly, most of the included studies were cross-

sectional studies. Therefore, the temporal relationship between NAFLD and urolithiasis could not be clearly established. Thirdly, the majority of the included studies were conducted in Asian countries, which may limit the generalizability of the observations to other populations. Fourthly, most of the primary studies included in this meta-analysis used ultrasonography to diagnose urolithiasis. Ultrasonography is a great tool to identify stones located in the kidney as well as pyeloureteral and vesicoureteric junctions but it often fails to detect ureteral calculi (unlike CT) [31]. Therefore, those studies may have missed some cases of urolithiasis, which may jeopardize the validity of their point estimates. This may also explain why subgroup analysis based on the methods used to diagnose urolithiasis found a higher magnitude of association among studies that diagnosed urolithiasis based on CT. Lastly, publication bias in favor of positive studies may have been present.

CONCLUSION

This study demonstrated a significantly increased risk of urolithiasis among patients with NAFLD. Insulin resistance, systemic inflammation and increased oxidative stress could be the link behind this association.

Conflicts of interest: We do not have any financial or non-financial potential conflicts of interest.

Authors' contributions. K.W., P.U. conceived and designed the study. K.W., S.L., P.P. and S.P. collected the data. K.W., P.P. and A.S. analyzed and interpreted the data. K.W., S.L. drafted the article. A.S., S.P., F.L. revised the article. K.W., S.L., P.P., A.S., S.P., F.L. and P.U. approved the final version of the manuscript. P.U. revised critically the manuscript.

Supplementary material: To access the supplementary material visit the online version of the *J Gastrointest Liver Dis* at <http://www.>

jgld.ro/wp/archive/y2018/n4/a13 and <http://dx.doi.org/10.15403/jgld.2014.1121.274.nac>

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Online Supplementary Data

Search Strategy

Database: Ovid MEDLINE

1. Nonalcoholic fatty liver.mp. or exp Nonalcoholic fatty liver disease/
2. fatty liver.mp. or exp fatty liver/
3. nonalcoholic steatohepatitis.mp.
4. steatohepatitis.mp.
5. or/1-4
6. urolithiasis.mp. or exp urolithiasis/
7. urinary calculi.mp. or exp urinary calculi/
8. kidney calculi.mp. or exp kidney calculi/
9. nephrolithiasis.mp. or exp nephrolithiasis/
10. bladder stone.mp. or exp urinary bladder calculi/
11. staghorn stone.mp.
12. ureteral calculi.mp. or exp ureteral calculi/
13. calcium oxalate stone.mp. or exp calcium oxalate/
14. or/6-13
15. 5 and 14

Database: EMBASE

1. Nonalcoholic fatty liver or Nonalcoholic fatty liver/exp
2. fatty liver.mp. or exp fatty liver/
3. nonalcoholic.mp. AND (steatohepatitis.mp. or exp steatohepatitis/)
4. steatohepatitis.mp. or exp steatohepatitis/
5. or/1-4
6. urolithiasis.mp. or exp urolithiasis/
7. nephrolithiasis.mp. or exp nephrolithiasis/
8. bladder stone.mp. or exp bladder stone/
9. staghorn stone.mp. or exp staghorn stone/
10. ureter stone.mp. or exp ureter stone/
11. calcium oxalate stone.mp. or exp calcium oxalate stone/
12. or/6-11
13. 5 and 12



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
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
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
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.	4
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.	4
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	4
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).	4-5
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.	4-5
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	4-5
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.	Table 1
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.	5-6



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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).	5-6
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	5-6
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
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).	Table 1
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.	6-7
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	7
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	Not applicable
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).	7-8
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).	8
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	8
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.	9

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(6): e1000097. doi:10.1371/journal.pmed1000097

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