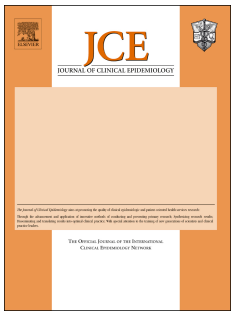

Frequent inappropriate use of unweighted summary statistics in systematic reviews of pathogen genotypes or genogroups

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PII: S0895-4356(19)30576-1

DOI: https://doi.org/10.1016/j.jclinepi.2019.11.009

Reference: JCE 10015

To appear in: *Journal of Clinical Epidemiology*

Received Date: 24 June 2019

Revised Date: 11 October 2019

Accepted Date: 12 November 2019

Please cite this article as: Tran L, Nhu Y M, Le Ba Nghia T, Hendam A, Vuong NL, Alzalal E, Sayed AM, Hussain MM, Sharma A, Tieu T, Mathenge PG, Hirayama K, Alexander N, Huy NT, Frequent inappropriate use of unweighted summary statistics in systematic reviews of pathogen genotypes or genogroups, *Journal of Clinical Epidemiology* (2019), doi: https://doi.org/10.1016/j.jclinepi.2019.11.009.

Frequent inappropriate use of unweighted summary statistics in systematic reviews of pathogen genotypes or genogroups

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Abstract

Objective: Our study aims to systematically assess and report the methodological quality used in epidemiological systematic reviews (SRs) and meta-analysis (MA) of pathogen genotypes/genogroups.

Study Design and Setting: Nine electronic databases and manual search of reference lists were used to identify relevant studies. The method types were divided into three groups: 1) with weighted pooling analysis (which we call MA); 2) unweighted analysis of the study-level measures, which we call summary statistics; and 3) without any data pooling (which we call SR only). Characteristics were evaluated using AMSTAR, PRISMA, and ROBIS tool. The protocol was registered in PROSPERO with CRD42017078146.

Results: Among 36 included articles, 5 (14%) studies conducted SR only, 16 (44%) performed MA, and 15 (42%) used summary statistics. The uni- and multivariable linear regression of AMSTAR and PRISMA scores showed that MA had higher quality compared to those with summary statistics. The SR only and summary statistics groups had approximately equal scores among three scales of AMSTAR, PRISMA and ROBIS. The methodological quality of epidemiological studies has improved from 1999 to 2017.

Conclusion: Despite the frequent use of unweighted summary statistics, MA remains the most suitable method for reaching rational conclusions in epidemiological studies of pathogen genotypes/genogroups.

Keywords: methodological quality, systematic review, summary statistics, meta-analysis, genotypes, genogroups.

Words count of abstract: 200 words.

Running title: Quality assessment of systematic reviews in epidemiological studies of genotypes/genogroups.

Introduction

Systematic review (SR) and meta-analysis (MA) have become cornerstones of evidence-based medicine, since they involve strategies to aggregate all relevant studies on a topic of interest [1]. They can provide robust inferences which help policymakers estimate benefits and risks of an intervention [2]. Currently, more than 10,000 MAs and qualitative SRs are published annually [3, 4]. However, substandard methodology and manipulation of statistical techniques in SR and MA are seldom considered [5].

Therefore, the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) statement, a 27-item checklist and a four-phase flow diagram, was developed as a tool for critiquing and enhancing the reporting of SRs and MAs [6]. In addition, the Assessment of Multiple Systematic Reviews (AMSTAR) tool is a 11-item checklist for multiple SRs and MAs, and provides for vigorous assessment of methodology and research reliability [7]. PRISMA and AMSTAR have been used to evaluate the research methodology in multiple medical fields, including surgery, pulmonary disease, telerehabilitation, nursing, gastroenterology and hepatology [8-10].

Due to the mounting number of epidemiological studies on genotypes or genogroups of pathogens, researchers and clinicians turn to SR and MA to keep up with the rising genomic knowledge [1]. However, there is a paucity of methodological investigations monitoring SR and MA [11]. In addition, there has been a call for appropriate assessment tools to examine potential bias in epidemiological studies [12]. Therefore, SR and MA of epidemiological genotypic studies should follow strict methodological appraisal to lessen any probable bias. When combining studies in meta-analysis, "an overall treatment effect is calculated as a weighted average of the individual summary statistics" [13]. Such weighting, based on each study's sample size and variation, is crucial to obtain a reliable summary of the evidence. However, in addition to those studies which do SR only (without any data pooling), several studies use simple summary statistics (e.g. unweighted mean) of the study-level measures, instead of MA methods [14-16]. For instance, Ali *et al.* reported simple summary statistics (mean and standard deviation) of study-level prevalences of hepatitis B virus [14] (although the abstract mentions weighting, this is not substantiated in the methods, and the numerical results, for example for the surgery studies, are unweighted). Due to the large number of SRs using non-MA methods, our study

aimed to systematically assess and evaluate the methods used in data analysis of epidemiological SRs of pathogen genotypes/genogroups.

Materials and methods

Search strategy

The protocol was designed and registered in the international prospective register of systematic reviews (PROSPERO) with ID number CRD42017078146. In September 2017, a systematic search was conducted in nine electronic databases: PubMed, Scopus, ISI (Web of Science), WHO Global Health Library, Virtual Health Library, Google Scholar, New York Academy of Medicine Grey Literature Report (NYAM) and System for Information on Grey Literature in Europe (SIGLE). The details of search terms used in each database are found in **Supplemental Table S1**. The search was performed by AMS and the references were stored using Endnote X7.0.1. We also performed a manual search in January 2018 to reach any possibly missed articles. Manual search was done by checking based on references of included articles, the related articles on PubMed search results and citation lists of included articles on Google Scholar [17].

Selection criteria

To be included in our study, the paper has to be either a SR or MA [18], which involved the prevalence or epidemiology of genotypes or genogroups of pathogens. No restriction was placed on publication date, language or disease area. A SR/MA article is defined as one or more of the following characteristics: (i) containing “systematic review” or “meta-analysis” on the title and abstract; (ii) containing PRISMA flow diagram; (iii) combining and summarizing all available research evidence from a systematic search fulfilling pre-determined criteria to answer a pre-defined question [1, 19-21]. The reason of exclusion was due to two main causes: (i) content not satisfying criteria: the article is not a SR/MA and (ii) inappropriate study design, such as: abstract-only articles, theses, conferences, letters, commentaries or books. The first stage of the screening process included the identification of titles and abstracts by three independent reviewers (EA, MMH and AMS). In the second stage, relevant articles proceeded to full-text

evaluation; the consensus was reached among three authors (AH, AS and AMS), otherwise consulted by the senior author (NTH).

Data extraction

A template in Microsoft Excel was built for pilot extraction and training. Afterwards, three independent reviewers (MNY, AH and LT) extracted the data and disagreements were resolved by discussion between authors and senior author (NTH). Authors extracted characteristics that included name and country of first author, year of publication, number of authors, impact factor (IF) of journal, and method types. Three main method types were defined in our study: 1-MA, a study conducted weighted pooling analysis; 2-Summary statistics, which used unweighted analysis of the study-level measures; 3-SR only, which is a SR study without any data pooling. Items of the AMSTAR and PRISMA checklists were assembled [22, 23]. The AMSTAR checklist is an 11-item list [7] and the PRISMA statement is a 27-item list [24]. Items of both tools were judged with; "Yes", "No", "Can't Answer" or "Not Applicable" (NA) response which meet "fulfilled", "not fulfilled", and "not clear" respectively. Any disagreements were resolved by discussion between the authors.

Quality assessment

The AMSTAR checklist was used to assess the methodological quality meanwhile the PRISMA checklist was used to assess reporting quality of the included SRs and/or MAs [6, 7]. In addition, the risk of bias was evaluated by three independent reviewers (TLBN, EA and LT) using Risk Of Bias In Systematic reviews (ROBIS) tool [25]. We focused on rating phase 2 and phase 3 of ROBIS, which involved a total of five domains with 24 signaling questions (SQ) and one overall judgment regarding the risk of bias for each domain. Phase 2 assesses the level of bias based on four domains: (1) study eligibility criteria (SQ=5), (2) identification and selection of studies (SQ=5), (3) data collection and study appraisal (SQ=5) and (4) synthesis and findings (SQ=6). In phase 3, each reviewer made a judgment about the overall risk of bias (domain 5, SQ=3). In each domain, the summary risk of bias was rated as "low", "high" or "unclear" through discussion by each reviewer in each included SR. Each SQ in each domain were answered as "Yes" = Good description/No bias, "No" = Bias, "Probably Yes", "Probably No", and "No Information". The total score for ROBIS was developed by the number of "Yes" answers in each question of each

domain [26, 27]. To have the scoring comparability with all three scales, the scoring determination of AMSTAR, PRISMA and ROBIS was "Yes" = 1 and "No" = 0.

Data analysis

Statistical software R version 3.4.4 was used for data analysis. (http://www.r-project.org/). Firstly, the characteristics of included articles, including the three main methods (MA, summary statistics and SR only), number of authors, IF of the journal, year of publication, and region of the corresponding author, were summarized using frequency and percentage for categorical variables. Mean and standard deviation (SD) for numeric variable were calculated. Polychoric correlation was calculated between the AMSTAR, PRISMA and ROBIS scores. Correlation coefficients have a value ranging between -1 (perfect negative correlation) and +1 (perfect positive correlation). We refer to negative correlation when coefficient was < 0, and to positive correlation when it as was > 0 [28]. We used linear regression model to evaluate the association between the articles' characteristics (IF of published journal, year of publication, region of corresponding author, number of authors, and study type) with AMSTAR, PRISMA, and ROBIS scores. Multivariable linear regression including all these covariates was then performed for each score to deal with potential confounders between them. Results from the uni- and multivariable models were reported as mean difference (MD), 95% confidence interval (CI), and the corresponding p-value. All raw data and R scripts were provided on GitHub with this link here https://github.com/Nguyenlamvuong/ORC_109.

Results

Study identification

Overall, we identified 3,543 potentially relevant reports by searching nine electronic databases and then removing 909 duplications using Endnote X7.0.1. After screening titles and abstracts of 2,634 references and removing 2,537 irrelevant reports according to the exclusion criteria, 97 articles were included for full-text screening. Of these, 68 articles were excluded due to exclusion criteria. From manual search of cited literature, 7 articles were added. Hence we included 36 studies in our analysis. The flow diagram of the review selection process is shown in **Figure 1**.

Characteristics of included articles

Major characteristics of the included articles, according to the method types (SR only, summary statistics and MA), are shown in **Table 1**. Of these 36 articles, 5 (14%) were SR only [29-33], 15 (42%) used summary statistics [14, 16, 34-46], and 16 (44%) used MA methods [47-62]. Details of all the included articles are listed in **Supplemental Table S2**. The publication years ranged from 1999 to 2017. Analysis over time demonstrates that, on all three measures, the methodological quality of epidemiological studies has improved from 1999 to 2017, in which AMSTAR is the lowest compared with PRISMA and ROBIS (**Supplemental Figure S1**). Overall, there is an average of 6.8 authors per paper and the mean IF is 3 ± 2.3 (**Table 1, Supplemental Figure S2**). The most frequent region is Asia (39%), followed by Europe (25%), North America (14%), with others contributing 22%.

In detail, the total AMSTAR, PRISMA and ROBIS scores of all included articles, according to the number of authors, are presented in **Supplemental Figure S3**. Most studies have fewer than 10 authors. The PRISMA and ROBIS scores, but not AMSTAR, tend to increase with the number of authors. The detailed scores by region are shown in **Supplemental Figure S4**. Articles from North America overall has the highest mean score, on all three scales. Studies from Europe have the lowest mean AMSTAR score while those from Asia have the lowest mean PRISMA and ROBIS scores.

Variables associated with AMSTAR scores

Supplemental Table S3 presents the reporting quality of individual AMSTAR items. The highest scoring items include two items, such as providing a priori design (item 1, 97.2%) and a comprehensive literature search performed (item 3, 88.9%). Some other items are poorly reported, including: providing a list of included and excluded studies (item 5, 36.1%), the scientific quality of the included studies (item 7, 38.9%), and an assessment of publication bias (item 10, 33.3%). In general, the AMSTAR score (mean ± SD) is 6.7 ± 2.7 out of a maximum of 11 (61% of items adequately reported, on average).

Results of uni- and multivariable linear regression with AMSTAR outcome are presented in **Table 2**. From 1999 to 2017, there is an increase of 0.33 points per year in AMSTAR scores (95% CI: 0.11 to 0.55, p=0.004). The summary statistics (non-MA) articles are associated with a

decrease in 2.65 AMSTAR points (95% CI: -4.37 to -0.92, p = 0.004) in univariable analysis and 3.04 points (95% CI: -4.97 to -1.10, p = 0.003) in multivariable analysis, compared with MA articles. Similarly, the SR only articles have 3.51 fewer AMSTAR points (95% CI: -5.97 to -1.05, p = 0.006) in univariable analysis and 3.69 fewer points (95% CI: -6.68 to -0.70, p = 0.017) in multivariable analysis, compared to MA articles.

Variables associated with PRISMA scores

Supplemental Table S4 shows the proportion of MAs that adequately reported each PRISMA item. Most are reported well, such as justifying a rationale for the study (item 3, 97.2%), identifying the objectives of the study (item 4, 94.4%), stating the eligibility criteria (item 6, 91.7%), providing a summary of the evidence including the main findings (item 24, 91.7%) and providing conclusions (item 26, 88.9%). Some other items are poorly reported, such as describing whether a protocol and/or registration (registration number) of the review was available (item 5, 25%), describing the assessment risk of bias across studies in the methods (item 15, 25%), stating risk of bias within studies in the results (item 19, 22.2%), and stating the funding (item 27, 36.1%). In general, the PRISMA score is 17.4 ± 4.6 out of a maximum of 27 (64% of items adequately reported, on average).

Uni- and multivariable regression results from PRISMA outcomes are shown in **Table 3**. From 1999 to 2017, there is an increase of 0.52 points per year in PRISMA scores (95% CI: 0.14 to 0.90, p= 0.009) in univariable analysis. Additionally, in multivariable analysis, there is an increase of 0.22 points in PRISMA score per additional author (95% CI: 0.02 to 0.43, p=0.035). Compared with MA articles, the summary statistics articles have 6.01 fewer points on average (95% CI: -8.60 to -3.43, p<0.001) in univariable analysis, and 5.75 fewer (95% CI: -8.94 to -2.56, p = 0.001) in multivariable analysis. Similarly, the SR only articles have 6.61 fewer points (95% CI: -10.29 to -2.93, p = 0.001) than MA articles in univariable analysis.

Association between AMSTAR, PRISMA, ROBIS scores

Polychoric correlation between each pair of AMSTAR, PRISMA and ROBIS scores is shown in **Supplemental Figure S5**. All three pairwise correlation coefficients are more than 0.4, suggesting a positive correlation among three scales of AMSTAR, PRISMA and ROBIS scores. The highest is 0.77 between ROBIS and PRISMA, then 0.61 between AMSTAR and PRISMA, and finally by 0.53 between ROBIS and AMSTAR.

Figure 2 presents that MA consistently has highest score meanwhile the summary statistics (non-MA) and SR only studies has lower and approximately equal scores on all three scales of AMSTAR, PRISMA and ROBIS.

Quality assessment based on ROBIS scores

Results of uni- and multivariable linear regression with ROBIS scores are shown in **Table 4**. Also, the ROBIS score is 13.9 ± 4.6 (range 2-24) out of 24 SQs. The ROBIS assessment to evaluate the risk of bias within a SR according to five domains is presented in **Figure 3**. With regard to domain 1, which assesses any concerns regarding specification of study eligibility criteria, 17 studies (47.2%) achieve a low risk of bias rating [30, 31, 35-38, 41, 48, 49, 51, 52, 54, 56, 57, 59, 60, 62]. In domain 2, identification and selection of studies, 20 studies (55.5%) have low risk of bias rating. In domain 3, which assesses methods used to collect data and appraise studies, 8 studies achieve a low risk of bias rating (22.2%) [32, 35, 49, 50, 52, 57-59]. With regard to domain 4, which assesses concerns regarding the synthesis and findings, 10 articles have low risk of bias (27.7%) [29, 31, 35, 38, 40, 46, 48, 52, 57, 58]. The final section (domain 5) provides a rating for the overall risk of bias of each SR: 20 are achieved a low rating (55.5%) [29, 31, 32, 35-37, 41-43, 45, 46, 48, 50, 52, 54-59], 8 are rated high (22.2%) [30, 34, 38, 51, 53, 60-62] and 8 are rated as unclear (22.2%) [14, 16, 33, 39, 40, 44, 47, 49].

Discussion

In this study, we describe the methodological reporting quality of methods used in epidemiological studies of pathogen genotypes/genogroups. Nearly half of the investigated SR articles employed simple descriptive analysis of study-level measures, rather than weighted meta-analysis methods. These articles had significantly lower reporting quality score (AMSTAR and PRISMA) compared to those using MA. Strong positive correlations between AMSTAR, PRISMA and ROBIS were also noted, in which, ROBIS is considerably correlated with PRISMA (0.77), followed by AMSTAR highly correlated with PRISMA (0.61), and finally AMSTAR moderately correlated with ROBIS (0.53), which indicates higher quality of AMSTAR is associated with higher score of ROBIS (lower bias). Similarly, Buhn *et al*. showed

that the percentage of "yes" scores of ROBIS ratings was strongly correlated with the AMSTAR ratings (correlation coefficient of 0.76) [27].

Besides the traditional SR and MA studies, we found an increase over time (1999-2017) in the use of unweighted summary statistics of study-level measures. We also found an increase in study quality over time. This finding is consistent with comparable studies of SRs and MAs in other fields such as gastroenterology, hepatology, cardiovascular diseases, vascular surgery and genetic association [63-66]. We did not find a significant correlation between the journal's IF and methodological quality of the SRs or MAs. Compared to the study by Ruano *et al.* where they analyzed 164 reviews, our study only included 36 studies, so the inability to identify an association may have been due to lack of power. This finding was in accordance with a report by Minelli *et al*. on the quality of MAs of genetic association studies [66]. Moreover, we also found a significant, but small positive correlation between PRISMA outcome score and the number of authors.

A limitation of our study was that it focused on the reporting quality of methodological details, which may not adequately reflect the quality of the underlying work done, as reported by Zavitsanos *et al.* in the field of urolithiasis [67]. In other words, a well-designed and well-conducted MA can be considered at high risk of bias if the description does not do justice to the methods used. Also, although ROBIS tool is considered as effective and reliable in measuring the overall risk of bias of SRs instead of only methodological quality, it requires greater expertise in reviewing due to more complex SQs than AMSTAR [27]. In addition, the use of scoring summary should be taken into account [68].

In this study, we utilized the PRISMA, AMSTAR and ROBIS checklist. There has been a critical appraisal of AMSTAR [69]. Therefore, there are certain limitations of the assessment instruments used in this paper that merits careful consideration. We recommend researchers in this field to adhere to certain guidelines or checklists, such as PRISMA or AMSTAR when conducting and reporting their research. This will ensure proper quality standard for all epidemiological articles of pathogen genotypes or genogroups. We found that the methodological qualities of studies employing MA method are better compared to the ones that employ SR only or summary statistics. We are uncertain about the reason behind this finding. We believe that the researchers pay more rigorous attention when conducting MA studies.

Conclusions

In summary, we found the methodological quality of articles using MA methods to be superior to that of SR only studies and to those using unweighted summary statistics, despite the growing frequency of the latter. There was an increase over time in the methodological quality of epidemiological studies of pathogen genotypes or genogroups, while still calling for further improvement. Authors, journal editors and readers should be attentive to the methodological quality of SRs and help maintain MA methods as one of the most effective tools in rationally identifying epidemiological evidence on pathogen genotypes or genogroups.

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528 **List of figures and tables**

529 *In manuscript*

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Supplementary files

Supplemental Figure S1. The AMSTAR, PRISMA and ROBIS score based on year of publication.

Supplemental Figure S2. The AMSTAR, PRISMA and ROBIS score based on impact factor of published journals.

Supplemental Figure S3. The AMSTAR, PRISMA and ROBIS score based on number of authors.

Supplemental Figure S4. The AMSTAR, PRISMA and ROBIS score based on the region of study.

Supplemental Figure S5. Polychoric correlation to compare scales between each pair of AMSTAR, PRISMA and ROBIS score.

Supplemental Table S1. Detailed search strategy for each database search.

Supplemental Table S2. Summary of included articles.

Supplemental Table S3. Distribution of individual questions in AMSTAR for all included studies.

Supplemental Table S4. Distribution of individual questions in PRISMA for all included studies.

560 **Table 1**. Principal characteristics of included articles.

Characteristics	All studies (N=36)	MA (N=16)	Summary statistics (N=15)	SR only (N=5)
Number of authors	6.8 (6.7)	5.3 (2.0)	9.3 (9.7)	3.6 (1.7)
Impact Factor	3.0 (2.3)	2.5 (1.1)	3.5 (3.2)	3.1 (2.6)
Year				
- 1999	1 (2.8%)	0 (0.0%)	0 (0.0%)	1 (20.0%)
- 2005	1 (2.8%)	0 (0.0%)	0 (0.0%)	1 (20.0%)
- 2009	2 (5.6%)	0 (0.0%)	2 (13.3%)	0 (0.0%)
- 2011	8 (22.2%)	2 (12.5%)	6 (40.0%)	0 (0.0%)
- 2012	2 (5.6%)	0 (0.0%)	0 (0.0%)	2 (40.0%)
- 2013	4 (11.1%)	1 (6.2%)	3 (20.0%)	0 (0.0%)
- 2015	2 (5.6%)	2 (12.5%)	0 (0.0%)	0 (0.0%)
- 2016	10 (27.8%)	6 (37.5%)	3 (20.0%)	1 (20.0%)
- 2017	6 (16.7%)	5 (31.2%)	1 (6.7%)	0 (0.0%)
Region				
- Asia	14 (38.9%)	8 (50.0%)	6 (40.0%)	0 (0.0%)
- Europe	9 (25.0%)	5 (31.2%)	3 (20.0%)	1 (20.0%)
- North America	5 (13.9%)	2 (12.5%)	1 (6.7%)	2 (40.0%)
- Others	8 (22.2%)	1 (6.2%)	5 (33.3%)	2 (40.0%)

561 *The summary statistics are absolute count (%) for categorical variables and mean (SD) for*
562 *continuous ones. Abreviation: SD= Standard Deviation; MA = Meta-analysis; SR = Systematic*
563 *Review.*
564

565 **Table 2.** Association of factors with AMSTAR scores.

	Univariable analysis			Multivariable analysis		
Characteristics	Coefficient	95% CI	p	Coefficient	95% CI	p
Impact Factor	0	-0.41 to 0.41	0.999	0.11	-0.28 to 0.50	0.568
Year	**0.33**	**0.11 to 0.55**	**0.004**	0.19	-0.08 to 0.47	0.164
Region:						
- Asia	reference		reference	reference		reference
- Europe	0.09	-2.32 to 2.49	0.94	-0.16	-2.20 to 1.88	0.871
- North America	0.04	-2.89 to 2.98	0.97	1.43	-1.72 to 4.59	0.36
- Others	1.52	-0.98 to 4.02	0.23	**2.98**	**0.76 to 5.20**	**0.01**
Number of authors	0.01	-0.13 to 0.15	0.85	0.02	-0.11 to 0.15	0.747
Method type:						
- MA	reference		reference	reference		reference
- Summary statistics	**-2.65**	**-4.37 to -0.92**	**0.004**	**-3.04**	**-4.97 to -1.10**	**0.003**
- SR only	**-3.51**	**-5.97 to -1.05**	**0.006**	**-3.69**	**-6.68 to -0.70**	**0.017**

566

567

568 **Table 3.** Association of factors with PRISMA scores.

	Univariable analysis			Multivariable analysis		
Characteristics	Coefficient	95% CI	p	Coefficient	95% CI	p
Impact Factor	-0.11	-0.80 to 0.57	0.741	-0.03	-0.67 to 0.62	0.936
Year	**0.52**	**0.14 to 0.90**	**0.009**	0.31	-0.15 to 0.77	0.176
Region:						
- Asia	reference		reference	reference		reference
- Europe	1.42	-2.67 to 5.51	0.49	0.13	-3.24 to 3.49	0.938
- North America	0.44	-4.55 to 5.43	0.86	2.91	-2.30 to 8.12	0.262
- Others	-1.73	-5.98 to 2.51	0.41	-0.25	-3.90 to 3.40	0.89
Number of authors	0.10	-0.13 to 0.34	0.38	**0.22**	**0.02 to 0.43**	**0.035**
Method type:						
- MA	reference		reference	reference		reference
- Summary statistics	**-6.01**	**-8.60 to -3.43**	**<0.001**	**-5.75**	**-8.94 to -2.56**	**0.001**
- SR only	**-6.61**	**-10.29 to -2.93**	**0.001**	-4.89	-9.82 to 0.05	0.052

569

570 **Table 4.** Association of factors with ROBIS scores.

	Univariable analysis			Multivariable analysis		
Characteristics	Coefficient	95% CI	p	Coefficient	95% CI	p
Impact Factor	0.20	-0.49 to 0.90	0.564	-0.14	-0.98 to 0.70	0.737
Year	0.10	-0.32 to 0.52	0.632	-0.01	-0.61 to 0.57	0.962
Region:						
- Asia	reference		reference	reference		reference
- Europe	1.46	-2.53 to 5.45	0.462	1.31	-3.04 to 5.66	0.542
- North America	3.37	-1.50 to 8.24	0.168	5.49	-1.25 to 12.22	0.106
- Others	-1.55	-5.70 to 2.59	0.451	-0.18	-4.90 to 4.54	0.938
Number of authors	0.093	-0.15 to 0.33	0.437	0.14	-0.13 to 0.41	0.288
Method type:						
- MA	reference		reference	reference		reference
- Summary statistics	-2.88	-6.14 to 0.37	0.081	-2.83	-6.95 to 1.30	0.171
- SR only	-4.55	-9.19 to 0.09	0.054	-5.62	-11.99 to 0.76	0.082

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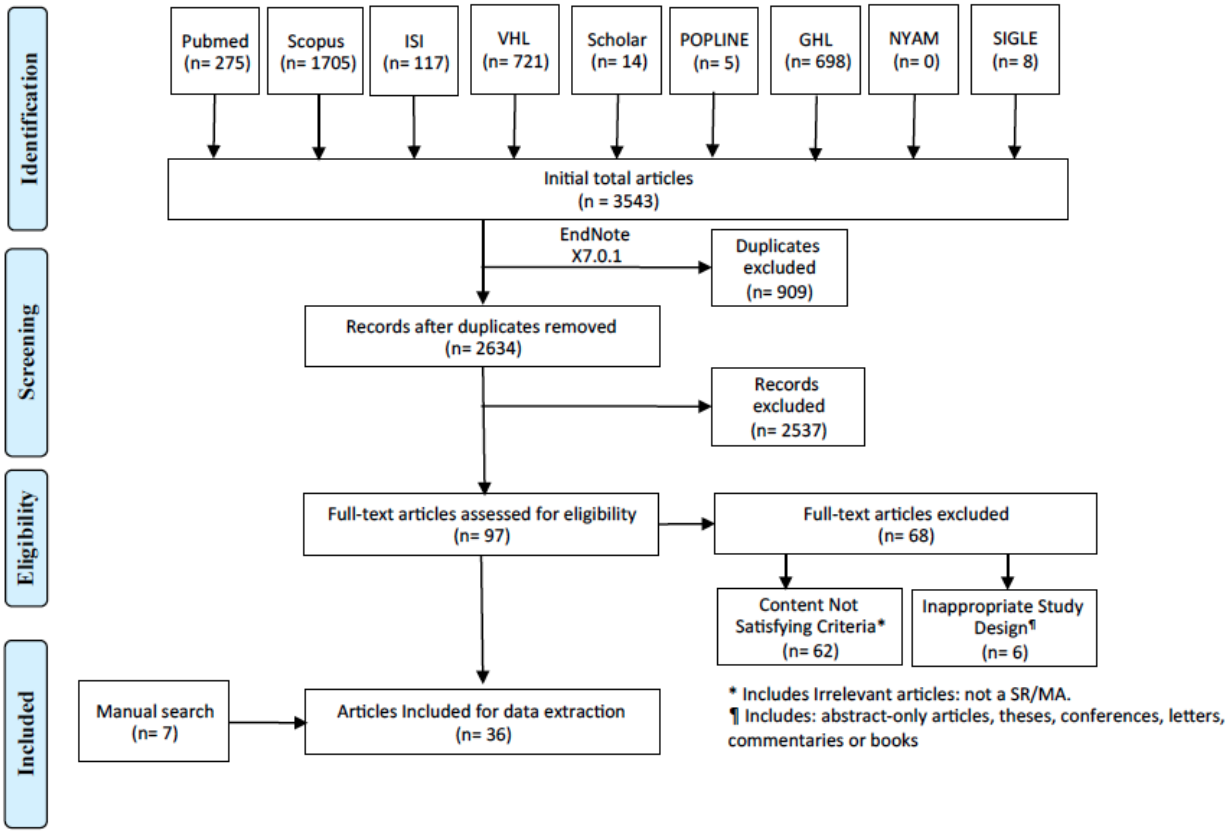
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Inappropriate Study Design¶ (n= 6)
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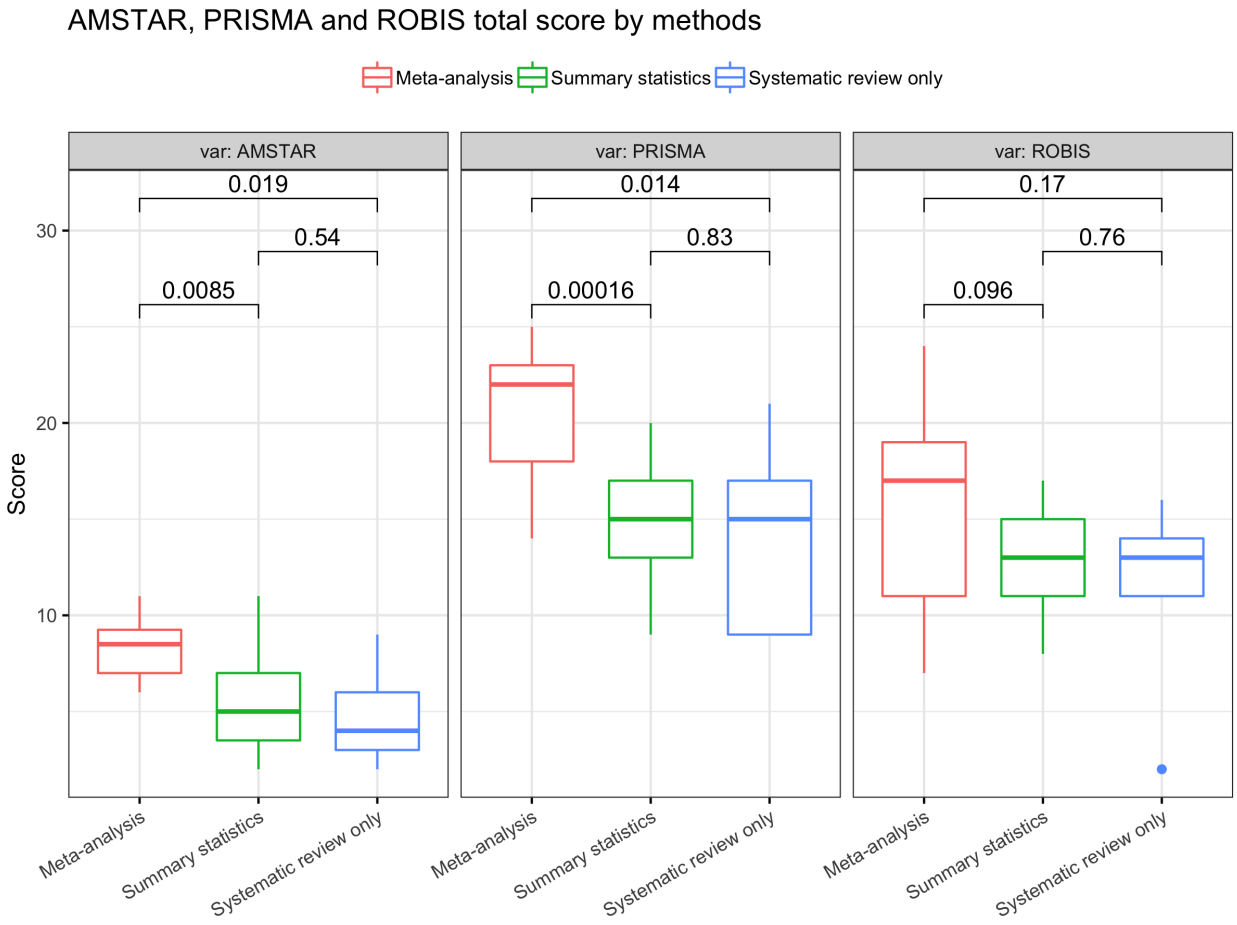
* Includes Irrelevant articles: not a SR/MA.
¶ Includes: abstract-only articles, theses, conferences, letters, commentaries or books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Summary statistics
Systematic review only
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var: PRISMA
var: ROBIS
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0.54
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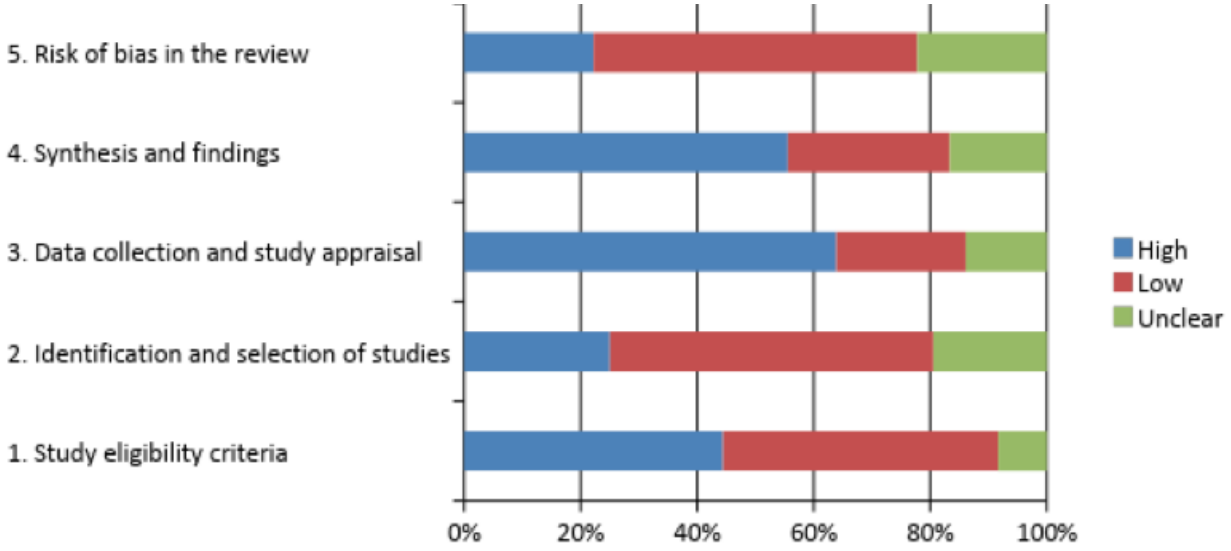

Conflict of interest

The authors declare there are no competing interests.

Funding

NA was supported by award MR/R010161/1, which is jointly funded by the UK Medical Research Council (MRC) and the UK Department for International Development (DFID) under the MRC/DFID Concordat agreement and is also part of the EDCTP2 program supported by the European Union.

Acknowledgements

The authors would like to thank Mansour Alhattab from Faculty of Medicine, Alexandria University, Egypt; Nassima Cherif Ouazzani from Faculty of Medicine, Aboubakr Belkaid University, Algeria; and Karim M Aly from Nasser Institute for Health and Research, Cairo, Egypt for their initial contributions to the study.