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Appraising the Quality of Systematic Reviews for Age-Related Macular Degeneration Interventions
A Systematic Review

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IMPORTANCE Age-related macular degeneration (AMD) is a leading cause of vision impairment. It is imperative that AMD care is timely, appropriate, and evidence-based. It is thus essential that AMD systematic reviews are robust; however, little is known about the quality of this literature.

OBJECTIVES To investigate the methodological quality of systematic reviews of AMD intervention studies, and to evaluate their use for guiding evidence-based care.

EVIDENCE REVIEW This systematic review adhered to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement. All studies that self-identified as a systematic review in their title or abstract or were categorized as a systematic review from a medical subject heading and investigated the safety, efficacy and/or effectiveness of an AMD intervention were included. Comprehensive electronic searches were performed in Ovid MEDLINE, Embase, and the Cochrane Library from inception to March 2017. Two reviewers independently assessed titles and abstracts, then full-texts for eligibility. Quality was assessed using the Assessing the Methodological Quality of Systematic Reviews (AMSTAR) tool. Study characteristics (publication year, type of intervention, journal, citation rate, and funding source) were extracted.

FINDINGS Of 983 citations retrieved, 71 studies (7.6%) were deemed eligible. The first systematic review relating to an AMD intervention was published in 2003. More than half were published since 2014. Methodological quality was highly variable. The mean (SD) AMSTAR score was 5.8 (3.2) of 11.0, with no significant improvement over time (r = −0.03; 95% CI, −0.26 to 0.21; P = .83). Cochrane systematic reviews were overall of higher quality than reviews in other journals (mean [SD] AMSTAR score, 9.9 [1.2], n = 15 vs 4.7 [2.2], n = 56; P < .001). Overall, there was poor adherence to referring to an a priori design (22 articles [31%]) and reporting conflicts of interest in both the review and included studies (16 articles [23%]). Reviews funded by government grants and/or institutions were generally of higher quality than industry-sponsored reviews or where the funding source was not reported.

CONCLUSIONS AND RELEVANCE There are gaps in the conduct of systematic reviews in the field of AMD. Enhanced endorsement of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement by refereed journals may improve review quality and improve the dissemination of reliable evidence relating to AMD interventions to clinicians.

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Supplemental content

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Age-related macular degeneration (AMD) is the leading cause of irreversible vision impairment in persons 50 years or older in developed countries.[1] This progressive condition can be clinically classified into early and late stages.[2] Late-stage AMD, being neovascular (choroidal neovascularization) or geographic atrophy, is typically associated with profound central vision loss and devastating impacts on quality of life.[3] It has been predicted that by 2020, AMD will affect approximately 200 million people worldwide.[4] Moreover, with aging demographics, the prevalence of AMD is forecast to double in the next 30 years.[4]

A range of therapies have been investigated for treating individuals with AMD. Approaches include photodynamic therapy, intraocular injectable agents, systemic medications, surgical interventions, radiotherapy, and oral vitamin and nutrient supplements. Since 2006, treatment options for choroidal neovascularization have vastly advanced with intravitreal therapeutics targeting vascular endothelial growth factor (VEGF) pathways.[5,6] Although there are currently no approved medical therapies for earlier stages of AMD or late-stage geographic atrophy, progression from early- to late-stage AMD occurs at a rate of about 4% per annum.[7] The risk of late-stage AMD can potentially be modified with nonmedical lifestyle interventions, including changes to diet and/or nutritional supplementation.[8] The Age-Related Eye Disease Study showed that a specific formulation of antioxidant vitamins and minerals could potentially reduce the risk of progression from intermediate-stage to late-stage AMD by 25% (ie, from an absolute risk of 28% to 20%) over 5 years.[9]

Evidence-based practice, commonly defined as "the conscientious, explicit and judicious use of current best (research) evidence in making decisions about the care of individual patients,"[10] is fundamental to providing the highest-quality clinical care. Moreover, the best available current research evidence should inform public health policy.[11] Given the vast and continuously increasing volume of scientific literature and the time constraints placed on decision makers, systematic reviews are frequently used to inform medical and public health decisions.[12] Systematic reviews intend to systematically identify, appraise, and synthesize findings from all relevant research studies relating to a health question. Given the importance of systematic reviews in health care, including their position at the peak of evidence hierarchy schema,[13] it is critical that systematic reviews are rigorous to avoid biased or inaccurate conclusions, particularly surrounding the efficacy and safety of interventions.

Recognizing a need to improve the conduct of systematic reviews, the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement was introduced in 2009.[14] PRISMA provides a framework for transparent and complete reporting and has been endorsed by many leading refereed health care journals. To support a consistent approach to critical appraisal, the Assessing the Methodological Quality of Systematic Reviews (AMSTAR) tool was developed[15] and validated[16] to assess methodological rigor. Furthermore, in 2011, an international prospective register of systematic reviews in health and social care, PROSPERO, was funded by the National Institute for Health Research (United Kingdom) with the intent of reducing the duplication of systematic reviews and potential reporting biases.[17]

Systematic review quality varies in several health disciplines, including radiology,[18] pediatric surgery,[19] emergency medicine,[20] and nursing.[21] However, to our knowledge, the methodological quality of systematic reviews relating to AMD interventions has not been investigated. Given the potential progression of AMD to profound vision loss and the associated individual and community burden from such vision impairment, it is imperative that AMD clinical care is timely, appropriate, and evidence-based. Essential to achieving this goal is that systematic reviews relating to AMD interventions are robust.

The primary aim of this systematic review was to investigate the methodological quality of systematic reviews of AMD intervention studies published in peer-reviewed journals and to evaluate their use for guiding evidence-based care. The secondary aim was to examine whether certain publication characteristics (eg, year of publication, AMD intervention type, impact factor of journal of publication, citation rate, funding source) were associated with review quality.

Key Points

Question What is the methodological quality of systematic reviews on age-related macular degeneration interventions?

Findings In this systematic review, review quantity is found to be increasing, but many age-related macular degeneration intervention reviews have major methodological limitations, and quality may not be improving over time. In particular, poor adherence to referring to an a priori design and reporting conflicts of interest was noted.

Meaning Clinicians need to be aware of potential methodological deficiencies between systematic reviews in the field of age-related macular degeneration; areas for improvement in the conduct and reporting of systematic reviews, which may have a positive impact on accurate dissemination of knowledge on age-related macular degeneration, are recommended in this analysis.

Methods

This systematic review was undertaken using the approach recommended in the PRISMA statement.[14] The protocol was prospectively published on PROSPERO (2017:CRD42017065453).[22]

Search Strategy

Comprehensive searches to identify all relevant studies were performed using (1) electronic databases from inception to March 31, 2017, in Ovid MEDLINE, Embase, PubMed, and the Cochrane Systematic Review Library (eMethods in the Supplement); (2) scanning references list of included studies for additional studies; and (3) searching PROSPERO for ongoing or recently published systematic reviews. The term *intervention* was defined as any manipulation applied with the intent of modifying the clinical outcome of AMD. Study inclusion and exclusion criteria are detailed in the **Box**.

Selection of Studies

After performing the searches, results were imported into EndNote, and duplicate entries were removed. The reference list was uploaded into Covidence online software (Veritas Health Innovation Ltd). A 2-stage process was used to select studies. First, 2 review authors (2 of L.E.D., L.J.D., K.K., M.-A.N.P., M.Y., and Y.B.

at a time) independently evaluated titles and abstracts. Full-text copies were obtained for articles assessed as relevant or possibly relevant by at least 1 reviewer. Two review authors (2 of L.E.D., L.J.D., K.K., M.-A.N.P., M.Y., and Y.B. at a time) independently assessed each full-text article and judged its eligibility. At each step, discrepancies in assessment were resolved by discussion and consensus among the authorship team, led by the principal investigator (L.E.D.).

Data Extraction

For each included study, 2 review authors (2 of L.E.D., L.J.D., K.K., M.-A.N.P., M.Y., and Y.B. at a time) independently extracted key data, including (1) publication details: year, journal (name and impact factor in the year of publication as listed in the Thomson Reuters InCites Journal Citation Reports), country of corresponding author, source of funding statement (dichotomous), source of funding (eg, industry, government, philanthropic), conflict of interest statement (dichotomous), conflict of interest type (eg, employee of company conducting study), citation rate (number of Google Scholar citations per year, for articles published before 2017) and (2) methodological details: years searched, number of studies included, population eligibility criteria (eg, stage of AMD), type of intervention and comparator, databases searched, critical appraisal tool used to assess study quality, whether a meta-analysis was performed, whether the PRISMA statement[14] was referred to, whether a summary of findings table was included, whether a statistically significant finding was reported, what the overall conclusion of the review was relating to the effectiveness, efficacy, and/or safety of the intervention, and how publication bias was assessed. Discrepancies were resolved by discussion and consensus among the review team.

Assessment of Methodological Quality

Two review authors (2 of E.M., L.E.D., L.J.D., K.K., M.-A.N.P., M.Y., and Y.B. at a time) independently assessed study quality using the 11-item AMSTAR tool in CrowdCARE (Crowdsourcing Critical Appraisal of Research Evidence: http://crowdcare.unimelb.edu.au, developed by L.E.D. and M.J.P.). For each domain, the review authors selected 1 of "yes," "no," "can't answer," or "not applicable" (eTable 1 in the Supplement). Assessment differences were resolved by consensus with the principal investigator (L.E.D.). A single point was awarded for each item that received a "yes" response; no points were awarded for "no," "can't answer," or "not applicable" responses. Total AMSTAR scores thus ranged from 0 to 11.

AMSTAR is one of the most frequently used appraisal tools for evaluating systematic review quality, despite having some acknowledged limitations, primarily related to its assessment of review reporting rather than methodological quality for some checklist items.[23] Although a more recent tool, ROBIS,[24] is now available, it was not considered appropriate for this study given the earlier time of the reviews evaluated.

Strategy for Data Synthesis

Tables and graphs were used to summarize descriptive data. Statistical analyses were performed using GraphPad Prism (version 7.0, GraphPad Software, Inc). Data normality was tested using the D'Agostino and Pearson omnibus test. For normally distributed data, 1-way analyses of variance were used to compare differences between group means. Pairwise comparison testing was performed using Fisher least square differences. Pairwise correlations were explored using Pearson correlation coefficient (r). A P value less than .05 was considered statistically significant. Unless otherwise specified, data are expressed as mean (SD).

Box. Study Inclusion and Exclusion Criteria

Inclusion Criteria

1. Self-identified as a systematic review in the title or abstract OR were categorized as a systematic review from a MeSH subject heading AND reviewed primary research studies.
2. Investigated the safety, efficacy, or effectiveness of any AMD intervention for any stage of the disease.

Exclusion Criteria

1. Nonintervention systematic reviews (ie, investigating the prevention, screening, diagnosis, etiology, or prognosis of AMD).
2. Systematic reviews of interventions for forms of macular degeneration other than AMD (eg, Stargardt disease).
3. Published in a language other than English.
4. Animal-based studies.
5. Systematic reviews of systematic reviews.
6. Intended to examine the state of the literature, in which participant outcomes were not the outcome of interest (eg, systematic reviews of tool validation, of the quality of studies in the field).
7. Conference abstracts.
8. Meta-analyses that did not incorporate a systematic review.
9. Outdated reviews (when an updated version of the same review was available and included).

Abbreviations: AMD, age-related macular degeneration; MeSH, medical subject headings.

Results

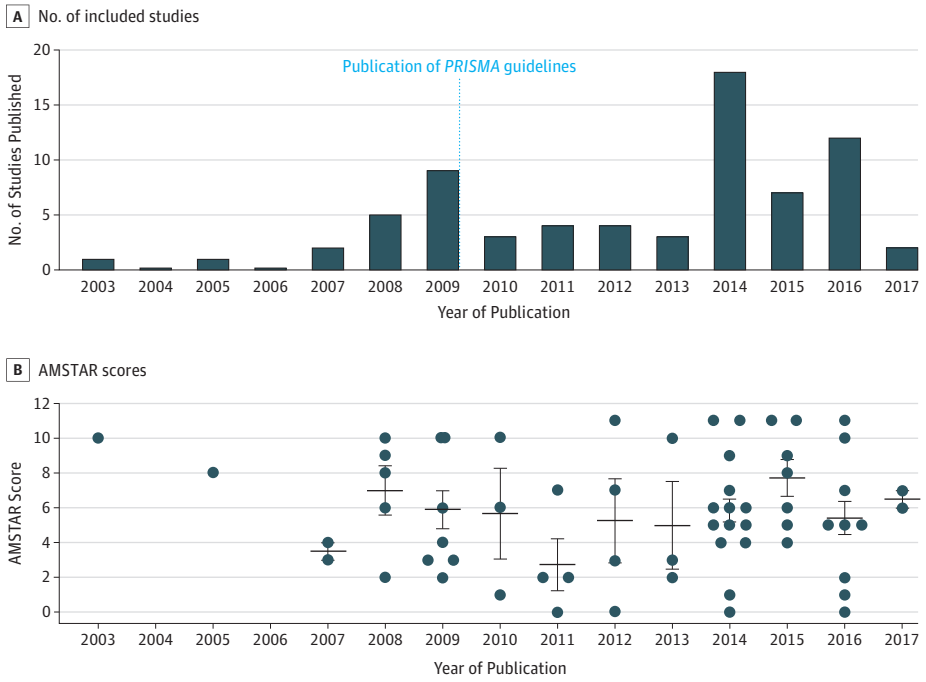
Search Results

As shown in the PRISMA diagram (eFigure in the Supplement), the electronic searches identified 983 potentially relevant publications, of which 271 duplicates (27.6%) were removed and 712 references (72.4%) proceeded to title/abstract screening. Full-text reports were obtained for 158 articles (16.1%) for further eligibility assessment; 87 studies (8.9%) were deemed ineligible (eTable 2 in the Supplement for a list of exclusions and the reference list), and 71 studies (7.2%) met the a priori criteria and were included[25-95] (eTable 3 in the Supplement for detailed study characteristics).

General Study Characteristics

Figure 1A shows the number of eligible studies published per year. The first systematic review relating to an AMD intervention was published in 2003. More than half of reviews in the field were published in the past 3 years. Study characteristics are summarized in the **Table**. The mean (SD) number of authors per article was 5.0 (2.9). Half of reviews had corresponding authors from the United States, China, and the United Kingdom; for most articles (53 [75%]), all authors had institutional affiliations in the same country.

Figure 1. Number of Included Studies and Overall Methodological Quality per Year of Publication



A, Number of systematic reviews published per year up to and including March 2017. The dashed vertical line represents the year that the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement was published. B, Assessing the Methodological Quality of Systematic Reviews (AMSTAR) score vs year of publication. Black bars represent mean (standardized error of the mean).

The reviews were published in a variety of scientific journals. The mean (SD) journal impact factor in the year of publication was 3.3 (1.8), and the number of citations was 8.6 (7.6) per year. Almost half (32 [45%]) of articles were published in ophthalmology journals, with about 20% (n = 15) in the *Cochrane Database of Systematic Reviews*. The reviews considered a range of AMD interventions; 63.4% (n = 45) evaluated anti-VEGF therapies, with 12% (n = 10) considering the role of vitamin and/or mineral supplementation. Overall, 47.9% of the reviews (n = 34) considered safety, in association with effectiveness or efficacy. Sixty-one percent (n = 43) of the reviews included a meta-analysis.

Of the 57 reviews published after 2009, 15 (26%) referred to the PRISMA statement. Of the 46 reviews published after 2011, none reported registration on PROSPERO. Funding sources and conflicts of interest for the systematic review itself were reported for most reviews.

Overall Methodological Quality of the Included Studies

Figure 1B shows the distribution of AMSTAR scores relative to year of publication. Overall, methodological quality was highly variable, spanning the spectrum of scores, from 0 (4 studies) to 11 (6 studies); the mean (SD) AMSTAR score was 5.8 (3.2). There was no significant linear trend between mean AMSTAR score and publication year (r = −0.03; 95% CI, −0.26 to 0.21; P = .83).

Factors Associated With Methodological Quality

Figure 2 shows data relating to the association between AMSTAR score and each of journal impact factor (Figure 2A), annual citation rate (Figure 2B), and journal of publication (Figure 2C). There was a moderately strong, positive correlation between journal impact factor and AMSTAR score (Figure 2A; r = 0.67; 95% CI, 0.52-0.78; P < .001) and a weak, positive correlation between citation rate and AMSTAR score (Figure 2B; r = 0.36; 95% CI, 0.14-0.55; P = .002). Considering only journals that had published at least 3 eligible studies, reviews in the *Cochrane Database of Systematic Reviews* were, on average, of higher quality than reviews published in other journals (Figure 2C; mean [SD] AMSTAR score, 9.9 [1.2], n = 15 vs 4.7 [2.2], n = 28; P < .05 for all comparisons).

On average, methodological quality was similar for reviews investigating different AMD interventions (**Figure 3**A). There was no significant difference (P > .05 for all comparisons) in AMSTAR score between reviews considering anti-VEGF agents (n = 47), vitamin and/or mineral supplements (n = 11), pharmaceutical agents (n = 4), radiation therapy (n = 3), photodynamic therapy (n = 3), or combination therapies (n = 3). Reviews incorporating meta-analyses had higher AMSTAR scores than those that did not (mean [SD], 7.0 [2.8] vs 4.0 [3.0], P < .001). The source of funding was associated with methodological quality (Figure 3B). Systematic reviews funded by government grants (mean [SD] AMSTAR score, 7.2 [3.1]) and/or institutions (mean [SD] AMSTAR score, 8.3 [2.9]) were, on average, of higher quality than those sponsored by industry (mean [SD] AMSTAR score, 4.1 [2.1]; P < .05 for both comparisons) or where the funding source was not reported (mean [SD] AMSTAR score, 4.4 [3.1], P < .05 for both comparisons).

Reporting of Individual AMSTAR Items

As shown in Figure 3C, the 3 most well-reported AMSTAR items were the use of appropriate methods to combine studies for meta-analyses (Item 9: 53 [98%] of the 54 studies that reported an intent to undertake a meta-analysis provided there were sufficient studies to pool the data), assessment of the scientific quality of the included studies (Item 7: 56 studies [79%]) and undertaking a comprehensive literature search (Item 3: 55 studies [77%]). The least well-reported domains were including a conflict of

Table. General Characteristics of Included Systematic Reviews

Characteristic	No. (%)
No. of authors	
1-3	23 (32)
4-6	29 (41)
>6	19 (27)
Country of corresponding author	
United States	14 (20)
China	12 (17)
United Kingdom	11 (15)
Canada	4 (6)
Australia	4 (6)
Brazil	4 (6)
Italy	4 (6)
Germany	4 (6)
Other[a]	14 (20)
International collaborative authorship	18 (25)
Systematic review type	
Effectiveness and safety	21 (30)
Safety	14 (20)
Efficacy	14 (20)
Efficacy and safety	13 (18)
Effectiveness	5 (6)
Effectiveness and cost-effectiveness	2 (3)
Other[b]	2 (3)
Journal of publication	
Cochrane Database of Systematic Reviews	15 (21)
British Journal of Ophthalmology	4 (6)
International Journal of Ophthalmology	4 (6)
PLOS ONE	4 (6)
Retina	4 (6)
Current Opinion in Ophthalmology	3 (4)
Graefe's Archive of Clinical and Experimental Ophthalmology	3 (4)
Ophthalmology	3 (4)
Investigative Ophthalmology and Visual Science	3 (4)
Other[c]	28 (39)
Category of AMD intervention	
Anti-VEGF agent(s)	45 (63)
Vitamin and/or mineral supplements	10 (12)
Pharmaceutical agents	4 (6)
Radiation therapy	3 (4)
Photodynamic therapy	3 (4)
Combination therapies	3 (4)
Laser treatment or surgery	3 (4)
Registered on PROSPERO (post-2011 reviews)[d]	0
Included a meta-analysis	43 (61)
Referred to the PRISMA statement (post-2009 reviews)[e]	15 (26)
Funding source reported	52 (73)
Conflict of interest reported for the systematic review itself	64 (90)

Abbreviations: AMD, age-related macular degeneration; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses; PROSPERO, International Prospective Register of Systematic Reviews; VEGF, vascular endothelial growth factor.

[a] Includes Thailand, Belgium, Ireland, Switzerland, France, Croatia, Portugal, the Netherlands, Israel, Korea, and Japan.

[b] Includes effectiveness, efficacy, and safety as well as psychological impact.

[c] Includes *Current Medical Research and Opinion; Health Technology Assessment*; *Sao Paulo Medical Journal*; *ClinicoEconomics and Outcomes Research*; *BMJ Clinical Evidence*; *BMJ Open*; *Drug Design, Development and Therapy*; *Brazilian Journal of Pharmaceutical Sciences*; *Strahlentherapie und Onkologie*; *American Journal of Cardiovascular Drugs*; *Acta Ophthalmologica*; *Advances in Therapy*; *Eye (London)*; *Klin Monbl Augenheilkd*; *Journal of Clinical Pharmacy and Therapeutics*; *Nutrients*; *Canadian Journal of Ophthalmology*; *Drug Safety*; *Journal of Ocular Pharmacology and Therapeutics*; *Journal of Ophthalmology*; *Biologics in Therapy*; *Clinical Ophthalmology*; *JAMA Ophthalmology*; *Ophthalmic Research*; and *Drugs & Aging*.

[d] n = 46.

[e] n = 57.

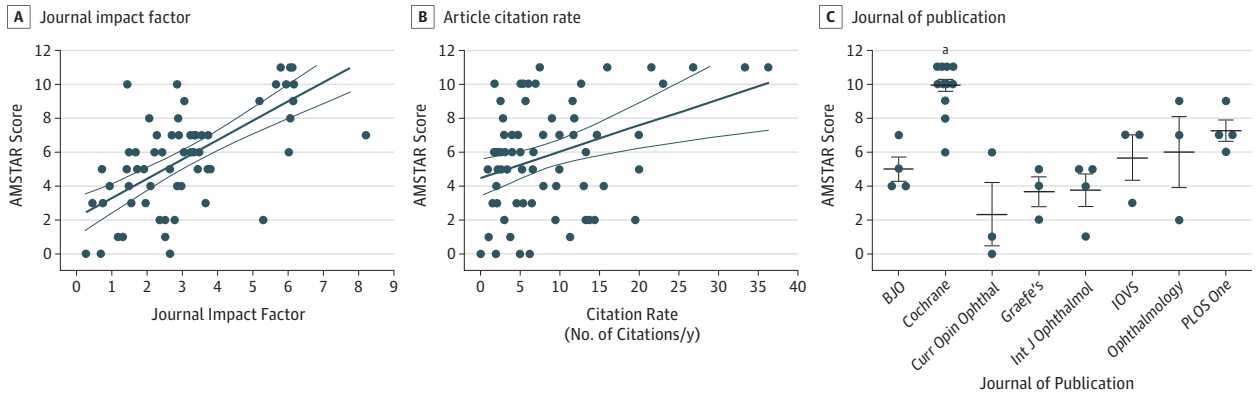
interest statement for both the review and included studies (Item 11: 16 [23%]), referring to an a priori protocol (Item 1: 22 studies [31%]) and providing details of included and excluded studies (Item 5: 22 studies [31%]).

Discussion

This systematic review examined the methodological quality of systematic reviews evaluating interventions for AMD. The analysis considered the association between several study characteristics (including publication year, type of intervention, journal, citation rate, and funding source) and review quality (as measured using AMSTAR[15]). Overall, methodological rigor has not changed substantially over the past decade. In general, there was poor adherence to AMSTAR items relating to referring to an a priori design, reporting conflicts of interest, and including a list of included and excluded studies. Systematic reviews funded by government grants and/or institutions were generally of higher quality than reviews sponsored by industry or where the funding source was not reported.

Systematic reviews are viewed as the highest level of evidence for considering the efficacy/effectiveness and/or safety of therapeutic interventions[13] and can thus be strongly influential for guiding evidence-based clinical care and health policy. However, as evident from this article, systematic reviews do not necessarily consistently provide high-quality evidence. A study described as a systematic review or meta-analysis does not necessarily assure rigorous conduct or reporting.[96] As with other

Figure 2. Publication Factors Influencing Overall Methodological Quality



A, Assessing the Methodological Quality of Systematic Reviews (AMSTAR) score vs journal impact factor, showing Pearson correlation (r = 0.67; 95% CI, 0.52-0.78; P < .001). B, AMSTAR score vs annual citation rate, showing Pearson correlation (r = 0.36; 95% CI, 0.14-0.55; P = .002). Only studies published prior to 2017 (n = 69) are shown. C, AMSTAR score vs journal of publication. Reviews published in the *Cochrane Database of Systematic Reviews* were of significantly higher quality than studies published in all other journals. Only journals that had at least 3 included systematic reviews are shown. Thinner lines in A and B represent 95% CIs.

BJO indicates *British Journal of Ophthalmology*; Cochrane, *Cochrane Database of Systematic Reviews*; Curr Opin Ophthalmol, *Current Opinion in Ophthalmology*; Graefe's, *Graefe's Archive for Clinical and Experimental Ophthalmology*; Int J Ophthalmol, *International Journal of Ophthalmology*; IOVS, *Investigative Ophthalmology & Visual Science*.

[a] P < .05.

study designs, such as randomized clinical trials, there is the potential for methodological flaws to induce bias, which may confound the reported findings.

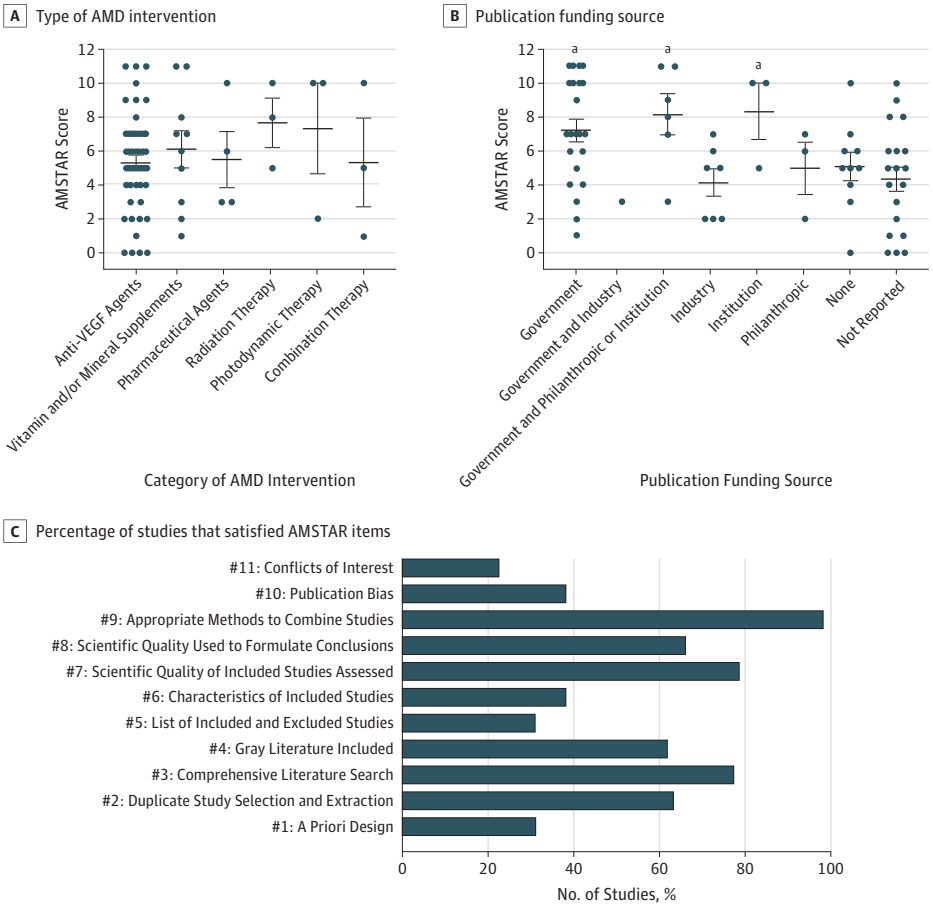
Critical appraisal, involving the careful and systematic evaluation of a study to assess its internal validity, value, and relevance, is an integral process to the practice of evidence-based medicine and applies equally to systematic reviews and individual research studies. Failure to consider systematic review quality and the citation of poorly conducted studies creates the potential for biased outcomes to gain traction, which subsequently risks the inappropriate translation of biased findings into health care practice and/or policy. We identified substantial heterogeneity in the methodological quality of published systematic reviews reporting on the efficacy and/or effectiveness and safety of AMD interventions, such that the quality encompassed the full spectrum of AMSTAR scores (from 0 to 11). Although the number of reviews has increased over time, this increase in quantity was not accompanied by an improvement in quality. This is despite introduction of the PRISMA checklist in 2009.[14] Only 1 in 4 studies published after 2009 referred to the PRISMA statement. This finding contrasts with observations in other medical fields, including radiology and critical care, where improvements in systematic review methodological quality have been demonstrated over time[97,98] and highlights an urgent need for enhanced systematic review quality in the field of AMD.

We observed a moderately strong correlation (r = 0.67, P < .001) between AMSTAR score and journal impact factor, suggesting that leading scientific journals are more discriminatory in their assessment of quality. The instructions for authors of journals that currently publish systematic reviews and/or meta-analyses and have an impact factor in the top 10% of journals in the discipline of ophthalmology (ie, *Ophthalmology*, *JAMA Ophthalmology,* and the *American Journal of Ophthalmology*), require a completed PRISMA checklist for manuscript submission. Reviews published in the *Cochrane Database of Systematic Reviews* were generally of the highest quality; this was the only journal in which reviews (n = 6) satisfied all 11 of the AMSTAR criteria. These findings support the widely accepted position that the Cochrane Collaboration have globally led standard setting for the undertaking and reporting of systematic reviews for therapeutic interventions, to provide robust evidence syntheses that minimize potential sources of bias[99,100]; similar findings relating to the quality of Cochrane reviews have been reported in other disciplines.[19,101]

One potential explanation for the quality of Cochrane reviews is their use of innovative new methods to support the conduct of systematic reviews. In the context of the Living Systematic Review Network,[102] a Cochrane-led community, automation of a number of components of systematic review workflows is contributing to both the timeliness and quality of reviews.[103] Continuous literature searching, identification of randomized clinical trials that satisfy eligibility criteria, and bias assessment[104] are benefiting from the application of automated algorithms based on information retrieval and text mining methods. We believe that there is scope to explore applying such methods for critical appraisal, for instance to support identification and assessment of key elements of the PRISMA checklist, such as PICO (Population, Intervention, Comparator, Outcome) characteristics,[105] and potentially even automation of scoring systems.

There was a relatively weak (r = 0.36, P = .002) correlation between AMSTAR score and annual citation rate. Reviews with the highest annual citation rates (>20 citations/y) were consistently of high methodological quality (AMSTAR scores ≥10). However, there was considerable variability evident for the citation of studies with poorer methodological rigor. While this observation may reflect a range of factors, including deficiencies in the search/retrieval process such

Figure 3. Other Factors Influencing Overall Methodological Quality



A, Assessing the Methodological Quality of Systematic Reviews (AMSTAR) score vs category of age-related macular degeneration (AMD) intervention. B, AMSTAR score vs source of funding. Studies funded either by government grants or institutions had significantly higher scores than reviews sponsored by industry or where the funding source was not reported. C, Plot showing the percentage of studies that satisfied each of the 11 AMSTAR items. Of the 15 reviews published in the *Cochrane Database of Systematic Reviews*, 6 satisfied each of the 11 AMSTAR items (ie, 11 of 11 score), and 5 satisfied 10 of the 11 AMSTAR items.

VEGF indicates vascular endothelial growth factor.

[a] $P < .05$ for both comparisons in panel B.

that authors are not identifying some reviews, it also potentially suggests that the authors may not be consistently critically appraising the scientific literature. To our knowledge, a study of the routine critical appraisal practices of researchers has not been previously undertaken but warrants consideration.

Although the type of AMD intervention considered in the review was not associated with methodological rigor, more than 60% of reviews considered the therapeutic effects of intravitreal anti-VEGF agents for the treatment of choroidal neovascularization in late-stage AMD. Most evaluated the effectiveness and/or safety of these interventions, highlighting significant, and arguably unnecessary, duplications in evidence synthesis efforts by research groups. Less than one-third of the reviews referred to an a priori protocol, which is important for reducing the likelihood of post-hoc adjustments to methods and/or outcome measures.[106] None of the reviews cited registration on PROSPERO.[17] It should be noted that Cochrane systematic reviews are based on a published, standardized protocol, although not registered on PROSPERO. In the context of clinical trials, global efforts have sought to enforce prospective trial registration to reduce publication and reporting biases and minimize unintended trial duplication. Relevant initiatives include the 2004 International Committee of Medical Journal Editors statement,[107] relating to compulsory, prospective trial registration for publication in leading medical journals (including *The New England Journal of Medicine* and *The Lancet*) and specifying this requirement in the Declaration of Helsinki.[108] Given that prospective registration is associated with the improved randomized clinical trial reporting,[109] a similar process involving a requirement for mandatory prospective registration of systematic review protocols, may be beneficial for achieving enhanced study quality, and minimizing unwarranted replication.

Systematic reviews funded by government grants and/or institutions were, on average, of higher quality than those sponsored by industry or where the funding source was not reported. The declaration of interest statement, to satisfy Item 11 of AMSTAR (ie, potential sources of support need to be clearly acknowledged in both the systematic review and the included studies), was not adequately provided in 77% of reviews (55 of 71). In medicine, including within the ophthalmic domain,[110] considerable attention has been directed toward highlighting the need for transparent reporting of conflicts of interest (to enable judgement of any potential external influences on the outcomes). Conflicts of interest, both financial and nonfinancial, are of concern as they may lead to relatively favorable interpretations and/or contribute to other sources of bias. The significance of this finding is arguably heightened in reviews lacking an a priori protocol, in which outcomes could be modified or redefined during the

review, potentially leading to a biased evidence synthesis. While commercial involvement in ophthalmic research, including in the field of AMD therapeutics, is not uncommon and in some cases essential, full disclosure of such relationships is critical for ensuring any relevant declaration of interest can be considered by the end user.

Limitations

An acknowledged limitation is that the review authors were aware of the authorship and journal of publication for each included study. Although this is standard practice in systematic reviews, there is the potential for bias resulting from personnel being unmasked. The expected significance of this effect was minimized by requiring the 2 review authors to reach a consensus assessment for each AMSTAR item.

Conclusions

This study highlights several key areas for improvement in the undertaking of systematic reviews relating to interventions for AMD. There is an urgent need for review authors to adhere to the PRISMA statement,[14] peer reviewers to critically appraise reviews against strict methodological criteria (such as that provided by AMSTAR), and journals to be judicious in their assessment of factors such as prospective registration, a priori protocols, and the reporting of conflicts of interest, to ensure that the rigor and transparency of evidence syntheses in the field is upheld. These improvements would be predicted to have a significant positive impact on the accurate dissemination of knowledge in the field of AMD, to clinicians, and in turn, the clinical care received by patients with AMD.

ARTICLE INFORMATION

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