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Literature review

Common mistakes in preparing systematic reviews and meta-analyses

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ABSTRACTS

Introduction. The number of systematic reviews and meta-analyses published in national and international journals is growing considerably. However, it is necessary to master the methodological aspects of this research phenotype for their correct development and interpretation.

Objective. To expose common methodological errors in the conduct of systematic reviews and meta-analyses.

Design and study context. Systematic searches were performed in PUBMED, Google Scholar, MEDLINE, Embase, LILACS, WHO, and SciELO to identify systematic reviews and meta-analyses with errors in their design. Each article was reviewed by the authors first separately and then jointly to discuss the results.

Conclusion. This research identifies a group of errors in the conduct of systematic reviews and meta-analyses. Methodological aspects are offered that can guide both reviewers and authors. Confusion with other types of reviews and incorrect statistical analysis stand out among the main difficulties.

Keywords: Systematic review; Meta-analysis; Methodological errors



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Introduction

Given the countless biomedical studies being published today, healthcare professionals face the uncertainty of how to choose the most effective interventions for patients; thus, evidence-based medicine emerges, whose most accurate definition highlights that clinical expertise must encompass and balance the patient's clinical condition, relevant research evidence, and the patient's preferences and actions. (1,2)

To obtain the best evidence and optimize time, systematic reviews and meta-analyses are developed, defined as a particular type of (secondary) research that seeks to offer a comprehensive, rigorous and inclusive view of a specific issue, providing a synthesis of evidence of the highest level of scientific quality. (3,4)

It is important to distinguish between a qualitative systematic review, which focuses on the exhaustive identification of all literature on a given topic, the evaluation of its quality, and the qualitative synthesis of its results, and a quantitative systematic review, whose highest expression, meta-analysis, incorporates a specific statistical strategy to synthesize the results in a single review. (3-5)

Currently, there is an increase not only in interest in consulting systematic reviews and meta-analyses but also an increase in this type of publication by various authors with or without research experience.

So much so, that the volume of systematic reviews and meta-analyses published in national and international journals is growing considerably. However, a mastery of the methodological aspects of this research approach is essential for its proper development and interpretation. With the aim of highlighting the most frequent errors in their design and interpretation, this study seeks to identify common methodological errors in conducting systematic reviews and meta-analyses.



Development

Study design and context Methodical searches were conducted in PubMed, Google Scholar, MEDLINE, Embase, LILACS, WHO, and SciELO to identify systematic reviews and meta-analyses with design flaws. Each article was reviewed by the authors first separately, and then the results were discussed together.

It should be borne in mind that a systematic review and meta-analysis is a research article with a complex methodology that involves the selection, review, critical appraisal, data collection and analysis of all available literature; it uses a predetermined, systematic and explicit method to answer specific research questions. (5,6)

Systematic reviews must follow a protocol designed to identify, evaluate, and synthesize all relevant evidence surrounding a specific research question. Their purpose is to provide a reliable and comprehensive summary of the existing literature to inform clinical practitioners about the best available evidence or future research. (7)

Keep the following steps in mind for its completion

Define the research question, delimit the search strategies, specify the selection criteria, design the data collection forms, write and register the review protocol, execute the search strategies, collect all references and abstracts, eliminate duplicate citations, review the titles and abstracts of the articles found, select the citations to include, retrieve the full texts of the articles and evaluate their inclusion criteria, contact subject matter experts, search for additional references, create the flow diagram, collect the information, and evaluate the quality of the studies. (7-9)

Likewise, prepare the database for analysis, develop the descriptive synthesis, meta-analyze, explore heterogeneity, assess the existence of publication bias, evaluate and interpret the evidence, and finally publish the systematic review. (7-10).

It could all be summarized in five steps: formulating the question, identifying potentially relevant studies, assessing the quality of the studies, synthesizing the results, and interpreting the evidence.



The above leads to the following observations: authors must possess robust knowledge of research methodology and biostatistics in general, in order to evaluate and select relevant articles (soundness and reliability); likewise, they must have mastery of the subject being investigated (not necessarily an expert, but being able to have their own academic judgment of what is being investigated) and finally have methodological discernment of this special form of research.

What are the common mistakes in conducting systematic reviews and how can they be avoided?^(7,11-14)

Inadequate data search Using inappropriate tools and search engines can lead to the selection of low-quality studies or a lack of relevant studies.

Clearly and precisely defining the research question using the PICO format (population, intervention, comparison, outcome) helps avoid errors in data collection. Conducting a thorough search across multiple databases and the grey literature allows for the establishment of clear and reproducible inclusion and exclusion criteria.

Incorrect assessment of the quality of studies Failure to properly evaluate studies can result in recommendations based on low-quality evidence. Reviews may include fraudulent studies and authors may have conflicts of interest that could bias the findings.

In this regard, authors must have a sufficiently robust understanding of research methodology and biostatistics to critically analyze the quality of the available literature. If they lack this knowledge, authors should consult a specialist in the field.

Incorrect data extraction and analysis This can lead to incorrect results or misinterpretation of the data. The solution is the same as mentioned before.

Lack of updates and duplication The long time it can take to conduct and publish a systematic review may not include recent primary studies.

One solution could be to conduct ongoing systematic reviews with continuous periodic updates. Teamwork, assigning tasks according to researchers' skills, and adherence to the protocol make research quick and efficient.



Incorrect synthesis and analysis: They can distort the interpretation of the evidence. This occurs when heterogeneous studies are combined without considering methodological or population differences.

How to conduct and write a meta-analysis? What are the common mistakes in conducting meta-analyses and how to avoid them?

Meta-analysis is a quantitative extension of systematic review, consisting of a powerful and sophisticated statistical technique used in research to combine and analyze the results of multiple independent studies on the same research question. Its main objective is to provide a more accurate estimate of the effect or association of interest by integrating the findings of individual studies, rather than relying solely on the results of a single study. (4-6,15-19)

A meta-analysis should be conducted within the framework of a statistical model. The model reflects how the studies were selected and determines how the results can be generalized. One of the following models is usually chosen: (7,8,16,19)

Random effects The model is applied when a set of studies is identified, research is selected from that set, and then the results of the analysis are used to generalize to that set. The word "random" reflects the assumption that the studies in the analysis constitute a random sample of all possible studies in this set. The word "effects" is plural because the effect (the impact of the treatment) is assumed to vary from study to study. (19)

The random-effects model works if all assumptions are met. It will work as expected if: A (a universe of all possible studies is listed), B (a random sample of studies is drawn from that universe), C (it is ensured that the studies included in the analysis are a representative sample of the studies performed), and D (a sufficient number of studies are available to obtain an accurate estimate of the between-study variance). (7-9,19)

The fixed-effect model This is used when all studies are based on the same population and are identical to each other in all relevant aspects. The results of the analysis apply to this specific population and cannot be generalized beyond it. The word "effect" is



singular because all studies share a common effect size, and "fixed" is assumed to mean common. It is sometimes called a common-effects model. (16,19)

The fixed effects model This approach is used when a specific set of studies is identified for inclusion in the analysis. As with the random-effects model, it is assumed that the effect size varies from study to study.

Unlike the random-effects model, these studies are not considered to be sampled from a larger universe. They are simply the only studies of interest. Statistics from the studies included in the analysis are presented, but the results are not generalized beyond them. (7,8)

The term "effects" is plural because the actual effect size varies from study to study. The term "fixed" reflects that these studies were not sampled from a larger population but were identified as the only studies of interest. (7,8, 16,19)

Errors in choosing a statistical model (16-19)

If all studies are based on the same population, the fixed-effects model should be used. If they are based on multiple populations, the random-effects model would be appropriate.

The choice of a statistical model should be based on an understanding of the sampling frame, not on a test of statistical significance. If it is unknown which model applies, one is simply guessing at numbers and no analysis should be performed. The fixed-effects model should not be used if generalization of the study is intended.

Common errors in random-effects models generally include: (A) it is not entirely clear which studies are included in the intended universe, (B) the studies conducted do not constitute a random sample of the intended universe, (C) the studies included in the analysis may not be representative of those conducted, and (D) there may not be a sufficient number of studies to obtain an accurate estimate of the variance between studies.

Knapp-Hartung adjustment: Generally, researchers calculate a confidence interval and a p-value using the Z distribution. In most cases, it would be preferable to apply the Knapp-Hartung adjustment. (19)



The confidence interval for the mean effect size in random-effects analysis is too narrow when based on the Z distribution. It would be better to use the Knapp-Hartung adjustment, which produces a wider (and more precise) interval. The adjustment applies to both the confidence interval and the null hypothesis test for the mean effect. (19-21)

Some researchers claim that they used the fixed-effects model because the random-effects model gives equal weight to all studies, and they want to give greater weight to larger studies. This is a mistake. (16,19)

The claim that the random-effects model assigns the same weight to all studies is incorrect. In reality, the weights are precisely calibrated to account for both within-study variance and between-study variance. This is appropriate when the goal is to make an inference about the set of comparable studies. (19-21)

Comparison of the results of both modelsA common mistake among researchers is to perform an analysis using both fixed-effects and random-effects models, and then compare the two results. Although some authors defend this approach as a kind of sensitivity analysis, its actual purpose is unclear. (19,20)

The problem with this approach is that, by changing the model, a whole set of elements changes, including the weights assigned to all studies, the width of the confidence interval, the ability to address the heterogeneity of effects, and the null hypothesis that addresses the significance test. (19,21)

Changing the model will have a major impact on the results

Researchers sometimes assume that the decision to use one model or another will have a major impact on the results. The reality is more complex; in fact, the effect of the model on the standard error depends on several factors. (19)

Meta-analyses with a large N will have good power

According to the random-effects model, statistical power usually depends on the number of studies, not the number of participants. When the variance between studies is considerable, the only way to obtain good power is often to include a large number of studies.



There is a misconception that meta-analysis should not be performed in the presence of heterogeneity. This is based on the erroneous premise that the goal of an analysis is always to estimate the average effect size. In fact, the goal of an analysis is to estimate the pattern of effects. If the effect size is reasonable across studies, it can be reported that the effect size is consistent, and the focus can then be on the average. If the effect size varies across studies, the magnitude of the variation and what this indicates about the usefulness of the intervention should be explained. (19,21)

The prediction interval

It addresses the question that arises when discussing heterogeneity. It indicates how the true effect size varies between populations, and it does so on a scale that allows for evaluating the usefulness of the intervention. The common mistake many researchers make is not reporting this range, especially in intervention studies. (19-23) Thus, for example, the effect is summarized in a forest plot showing a point estimate with a confidence interval. Researchers sometimes assume that the confidence interval corresponds to the spread of the effects. In a variant of this error, the forest plot is used to show one confidence interval for the fixed-effects model and a second (wider) confidence interval for the random-effects model. On the other hand, readers sometimes assume that the wider confidence interval for the random effects corresponds to the spread of the effects, which in both cases is a fundamental error. (19,20)

Errors in the use of the I^2 statistic

The I^2 statistic is commonly believed to indicate the variability in effect size between studies. In some cases, this belief is deeply ingrained, with I^2 values of 25%, 50%, and 75% considered to reflect low, moderate, and high levels of dispersion, respectively. While this interpretation of I^2 is widespread, it is incorrect and reflects a complete misunderstanding of this index. (19)

Heterogeneity refers to how much the true effect size varies between studies. This is addressed by the prediction interval, which indicates (for example) that the true effect size in most populations lies between 0.05 and 0.95. It is not addressed by the I^2



statistic, which indicates what proportion of the variance in observed effects reflects the variation in true effects, rather than sampling error. It does not indicate how much variation exists, and therefore its misuse can lead to erroneous conclusions and interpretations. (7,19-22)

Therefore, it is important to understand that I^2 is a useful summary of the impact of heterogeneity and should be presented in meta-analyses in preference to the heterogeneity test. However, classifying heterogeneity as low, moderate, or high based on the I^2 index is a common error. (19)

Use the p-value as an index of heterogeneity

Another mistake researchers make is assuming that the heterogeneity test reflects the amount of dispersion in the effects. A non-significant p-value is interpreted as evidence that the effects are consistent, and a significant p-value is considered evidence that the effects vary significantly. This is a regrettable error. (19)

The p-value of a heterogeneity test depends on the estimated magnitude of heterogeneity, the precision of the individual studies, and the number of studies included in the analysis. The value may be statistically significant when the estimated heterogeneity is minimal. Conversely, it may not be statistically significant when the estimated heterogeneity is large. Therefore, the p-value should never be used as an indicator of the magnitude of heterogeneity. (19,23)

Use the Q value as an index of heterogeneity

One mistake is to use the Q-value as an index of dispersion and assume that a high Q-value reflects a substantial amount of heterogeneity. The Q-value for a test of heterogeneity depends on the magnitude of the observed heterogeneity, the precision of the individual studies, and the number of studies included in the analysis. (19)

The Q-value can be high when the estimated heterogeneity is minimal. Conversely, the Q-value can be low when the estimated heterogeneity is high. Therefore, the Q-value should never be used as a proxy for the magnitude of heterogeneity. (19)

Errors related to statistical significance tests



When the effect size is consistent across studies, the situation in a meta-analysis is essentially the same as in a primary study. When the analysis concerns the usefulness of an intervention, the null hypothesis testing paradigm addresses a question that is not actually relevant (Is the effect size precisely zero?), whereas effect size estimation addresses the question that is relevant (What is the magnitude of the effect?). (19,23,24)

Currently, there is broad consensus that researchers should generally focus on effect size estimation when assessing the impact of an intervention. While guidelines now recommend (or require) this shift for most analyses, the transition in primary studies has been slow. In the case of meta-analyses, focusing on effect size estimation should be more natural, as these are based on the magnitude of the effect. (19,23,24)

When using random-effects analysis, if the effect size tends to be larger in small studies, this could be due to publication bias, but it could also reflect that the effect size is actually larger in small studies. (19,24)

Publication bias

Publication bias refers to the concern that studies reporting relatively large effects are more likely to be published than studies reporting smaller effects. (19,23,24)

Confusing bias with the small study effect: When a test for publication bias is statistically significant or indicates that studies are missing, the researcher often concludes that this is evidence of publication bias. (19,25-27)

When using random-effects analysis, if the effect size tends to be larger in small studies, this could be due to publication bias, but it may also reflect that the effect size is actually larger in small studies. The procedures described here do not allow us to distinguish between these two possibilities. (19,25-27)

When a test for publication bias is statistically significant, researchers sometimes conclude that meta-analysis is not useful. However, the presence of bias does not automatically invalidate the results. (19)



Comprehensive meta-analysis software Locating and mastering a statistical package that allows meta-analysis is essential to ensure that the results are robust and unbiased.

How to report the results of a meta-analysis

Sometimes researchers intend to address one question, but actually report statistics that address another question. They intend to ask about the mean effect size, but instead focus on a significance test and do not discuss the clinical or substantive significance of the effect. Or, they intend to ask how much the effects vary, but then report statistics that do not actually provide this information. (19,28,29)

Undoubtedly, systematic reviews and meta-analyses have gained prominence in biomedical specialties in recent years. The conclusions drawn from a meta-analysis allow researchers to synthesize the evidence on a given topic. Likewise, they are up-to-date tools for synthesizing the available evidence, enabling healthcare professionals, particularly those in training, to enhance their professional development.

However, it is important that researchers conducting these types of studies are aware of the aforementioned errors and take steps to avoid them. This requires training in research methodology in general and in conducting systematic reviews and meta-analyses in particular, while users of systematic reviews and meta-analyses should have at least a basic understanding not only of the studies themselves but also of their quality. They can also use tools that help identify some of these problems. The best-known tools are PRISMA for reporting quality; AMSTAR 2 for methodological quality; and ROBIS for assessing the risk of bias. (30-34)

At the national level (national journals), there is a trend toward publishing articles classified as systematic reviews and meta-analyses. However, as at the international level, these publications contain a number of errors, among which the following stand out:

Classification error: confusing systematic reviews and meta-analyses with other types of reviews (bibliographic, narrative, scope, among others).



The existence of a protocol prior to the development of the research is not declared: this is a key element for success, as it is a systematic process that allows researchers to collect, evaluate, and synthesize information on a specific topic. Like any research protocol, it includes several stages (planning, searching, evaluating, and synthesizing the findings). It ensures the rigor of the research, can identify under-researched areas, and support future studies. (19,34)

Methodological errors The PICO question was not stated, the stated objectives were not developed in accordance with this type of study, and the methods used were not described. Statistical tests were used incorrectly, leading to the publication of spurious results.

The presentation of the results: it is not done correctly and the results are frequently misinterpreted, which limits the evaluation by reviewers and readers.

Some journals limit the number of authors to three: systematic reviews and meta-analyses are complex investigations that require a significant number of authors depending on the topic investigated, so reducing it to only three authors, as if it were a bibliographic review, is a big mistake.

The researchers in this study believe that this brief review of the topic could help journal editors and reviewers identify errors in the execution and interpretation of systematic reviews and meta-analyses, while providing authors with a useful tool to delve deeper into methodological aspects and obtain more precise findings and robust conclusions in this particular type of research. They recommend reviewing the article by Kanukula et al. entitled: "Identification of application and interpretation errors that can occur in pairwise meta-analyses in systematic reviews of interventions: a systematic review." (35)

Ethical considerations

This study is a narrative review of the scientific literature based exclusively on information previously published in academic and scientific sources. Consequently, no direct intervention was performed on humans or animals, nor were any identifiable individual clinical data used.



Conclusions

This research identifies a group of errors in conducting systematic reviews and meta-analyses. Methodological aspects are offered that can guide both reviewers and authors. Confusion with other types of reviews and incorrect statistical analysis stand out among the main difficulties.

The list of errors and their possible solutions presented should be kept in mind to avoid drawing spurious conclusions.

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Conflicts of interest

The authors declare that there are no financial, personal or professional conflicts of interest that may have influenced the performance or interpretation of the results of this study.

Authorship contribution

Alexis Álvarez Aliaga: conceptualization, formal analysis, research, methodology, project management, formal analysis, research, writing – original draft, writing – revision, editing, supervision and validation.

Liannys Lidia Naranjo Flores: resources, formal analysis, research, methodology, data curation, writing – review and validation.



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