Chapter 06 / Capítulo 06

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Systematic Reviews and Meta-Analyses / Revisiones Sistemáticas y Meta-Análisis

Systematic reviews (SRs) and meta-analyses (MAs) represent advanced scientific studies in which the original primary studies are examined as units of analysis. These methodologies are now key tools for summarizing existing scientific information, improving the validity of individual research conclusions, and identifying areas of uncertainty that would benefit from future research. In addition, they are considered the highest level in the hierarchy of evidence and play a crucial role in clinical decision-making within the framework of Evidence-Based Clinical Practice (EBCP). The central purposes of this topic include: providing the fundamentals for conducting a systematic review and/or meta-analysis, and offering a conceptual guide for the critical evaluation of these studies.

6.1. Concept and nomenclature

Systematic Reviews (SR) and Meta-Analyses (MA) are forms of scientific research in which original primary studies are analyzed to answer specific research questions using systematic, explicit, and reproducible methods. They are categorized as secondary research, i.e., research on previous research. An SR that includes a quantitative synthesis of the results of original studies is known as a quantitative SR or MA. However, there are situations in which it is not appropriate to combine the results; in such cases, if the appropriate protocol is followed, the study is considered a qualitative SR. In summary, all MAs are SRs that include a quantitative synthesis, but not all SRs are MAs.

From a formal perspective, MAs follow a rigorous protocol that encompasses all phases of a traditional research project: formulating a research question, conducting a systematic and comprehensive search for relevant articles, selecting articles according to explicit criteria, evaluating the quality of the original studies, synthesizing the data to calculate combined results, and interpreting them to summarize scientific evidence and guide future research.

Generally, an MA combines aggregated data from published studies. Still, sometimes it may include individual patient data from the original studies, known as individual patient data MAs, which are considered the gold standard in SRs. It is crucial to differentiate SRs (both qualitative and MAs) from Narrative or traditional Reviews, which do not follow a systematic and rigorous process. The latter are more akin to scientific literature based on authors' opinions rather than a formal research process. The figure below highlights the differences between these two types of reviews.

The growing importance of meta-analyses (MAs) is due to several significant advantages: i) They facilitate greater generalization or external validity of results, as they include samples from different contexts and populations, compared to individual studies; ii) They offer higher statistical power due to larger sample sizes, which helps identify differences in effects that may not have been detected in individual studies; iii) The increase in sample size improves the precision of the effect estimate, resulting in tighter 95 % confidence intervals (95 % CI).

However, MAs also have important limitations: i) They are subject to potential biases that may affect the final result, such as publication, location, and inclusion biases; ii) The validity of the results depends on the quality of the individual studies analyzed and may be affected by

methodological decisions made during their conduct, such as the formulation of the research question, the search strategy, and the inclusion and exclusion criteria, among others; iii) If there is a high degree of heterogeneity among the studies analyzed, it may be difficult to interpret the results.

Caracteristica	Narrative Review	Systematic Review
Research question	Unstructuread, not specific	Structured question, well-defined clinical problem
Search for **articles** and their sources	Not detalled and unsystematic	Structured and explicit search
Selection of articles of interest	Not detalled and unreproducible	Selection based on explicit criteria uniformly applied to all articles
Evaluation of information quality	Absent	Structured and explicit
Synthesis	Often qualitative summary	Qualitative and/or quantitative summary
Inferences	Generally based on authors' opinion and ad/or evidence found from a non-exhaustive search	Usually based on the evidence

Figure 6.1. Differences between narrative and systematic reviews

6.2. Stages of a systematic review

In short, a systematic review comprises the following phases: establishing the research question and criteria for including or excluding studies; identifying and selecting relevant studies; collecting information from the original studies; analyzing and presenting the findings; and finally interpreting those findings.

6.2.1. Definition of the research question

The first essential step is to formulate the research question properly. Generally, this should be clear and well structured, incorporating the essential components of the PICO format (Population, Intervention, Comparison, Outcomes). At this stage, it is crucial to decide which study designs to include in our review, depending on the nature of the question to be investigated. For example, to evaluate the effectiveness of an intervention, as in the case mentioned above, randomized clinical trials are the obvious choice. This approach is similar when evaluating the reliability and safety of a diagnostic test, although cross-sectional studies are even more common. In systematic reviews that analyze community or public health interventions, or to evaluate the long-term results of an intervention, especially in terms of safety, community trials and observational studies are often more relevant.

6.2.2. Search and selection of relevant studies related to the research question

This section covers several relevant elements that underpin the construct.

Identification of important ítems is crucial to collect as many primary studies as possible on the topic of interest. This helps reduce random error and, more importantly, minimize

publication bias. Often, studies with inconclusive or negative results are not published, and their omission could skew the results of a systematic review. This phenomenon is known as publication bias. The relevance of this bias lies in the fact that systematic reviews that exclude unpublished studies tend to exaggerate the association between exposure and the event of interest. In extreme cases, they could even present ineffective treatments as effective. The presence of publication bias can be assessed using various graphical or statistical methods; the funnel plot is the best-known. A symmetrical inverted V-shaped graph suggests a probable absence of publication bias. Conversely, an asymmetrical graph indicates the possible presence of this bias. The interpretation of an asymmetrical graph suggests that there may be unpublished studies or trials with negative results that, if included, could contradict the meta-analysis's positive findings.

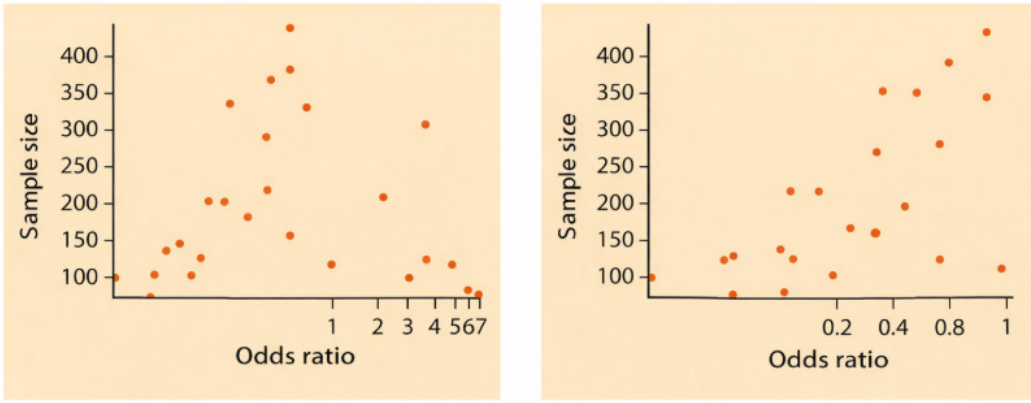

Figure 6.2. Distribution

The next step is to determine where to find primary studies. For more information on this topic, we recommend consulting the guidelines on bibliographic searches. Limiting your search to electronic databases may not be the best option for all topics. Sometimes it is advisable to use additional strategies to discover unpublished studies or gray literature. This process is often among the most demanding, as it may involve manually reviewing journal abstracts and conference proceedings, as well as contacting experts in the field, pharmaceutical companies, and others. The Cochrane Collaboration has led an international initiative to create a registry of controlled clinical trials, formerly known as the Cochrane Controlled Trials Register and now called CENTRAL

After identifying titles and abstracts, an initial screening of potentially suitable articles should be carried out. It is recommended that two independent reviewers perform this selection to improve the reliability and accuracy of the process. It is also crucial to assess agreement among reviewers using the kappa statistic for each criterion on the selection sheet. This index, in simple terms, assesses the level of agreement between reviewers. Finally, it is essential to properly document the entire study search and selection procedure, showing in a flowchart the articles found at each stage, along with those discarded and the reasons for their exclusion.

Extraction of results and data from primary articles or studies: At this stage, it is crucial to ensure maximum accuracy in collecting information from each selected study, so it is advisable to perform data extraction twice. In summary, the data extraction sheet generally covers: A)

Data on patients, the intervention of interest, the control intervention, and the study design; B) Information related to the results; and C) Details on the methodological quality of the study.

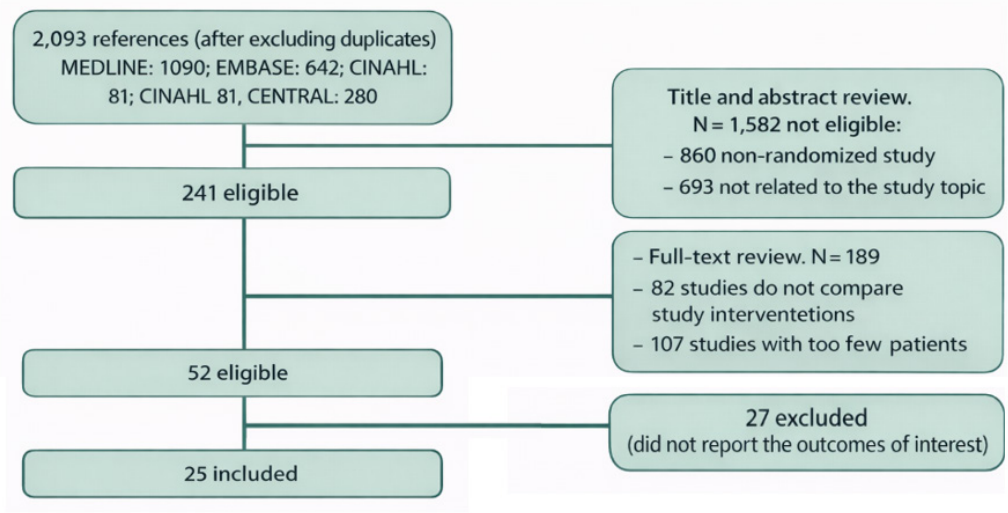

Figure 6.3. Selection process (example)

Assessing the methodological quality of a study is crucial, though the process is debated. There is no universal agreement on the best way to assess a study's methodological quality. A common approach is the use of quality scales. Several scales are available, with the JADAD scale among the best known and most widely used due to its simplicity, especially in Cochrane meta-analyses. Recently, a new system called GRADE (Grading of Recommendations Assessment, Development, and Evaluation) has been introduced to quantify the methodological quality of the studies included.

There is also a lack of consensus among the scientific community on how to assess methodological quality. Some experts argue that this assessment should be used as a selection criterion, excluding articles that do not meet a minimum quality threshold. On the other hand, some believe that these studies should be included, but that their impact on the final results should be assessed through sensitivity analyses or adjusted according to their quality.

Presentation of results: a meta-analysis (MA) conceptually integrates the results of two or more studies that address the same intervention and have measured the same outcome variables.

The process is not limited to calculating a simple arithmetic mean of the results but is based on a weighted mean. This weighting usually depends on the sample size of each study, giving more weight to those with greater informational content, i.e., those that are larger and/or have more events. In the statistical analysis of an MA, it is crucial to assess the extent to which the results of the various primary studies can be summarized in a single effect measure and whether the variability between them is greater than expected by chance. This assessment, based on heterogeneity analysis, can be performed using statistical or graphical methods. If there is considerable variability (heterogeneity) between studies, it may not be appropriate to combine them statistically. In such cases, the results should be presented independently, and the characteristics of the individual studies should be described in tables.

There are two main models for combining results statistically: the fixed-effects model and the random-effects model. The fixed-effects model assumes that the treatment effect is constant across studies, whereas the random-effects model allows it to vary randomly across studies. In other words, the fixed-effects model considers only one source of variability (the study-level), whereas the random-effects model introduces additional variability between studies. As a practical result, the random-effects model tends to generate more conservative estimates (with wider confidence intervals) of the combined effect. The choice between these models depends on analyzing the similarities and differences among the studies to be combined, although both models are often used.

The "heterogeneity" between studies refers to the fact that, after adjustment, the effects of the intervention reported in individual studies vary more than would be expected by chance. This may be due to differences in study design, data collection methods, analyses used, or characteristics of the populations studied, resulting in "different" intervention effects across studies. There are several statistical indices for measuring heterogeneity; the best-known are the Q, H, and I statistics. I is particularly intuitive, indicating the percentage of the total variability in intervention effects (between studies) attributable to true heterogeneity rather than chance. Generally, and I of 25 % indicates low heterogeneity, 50 % moderate heterogeneity, and 75 % high heterogeneity.

To graphically visualize the results of a meta-analysis, a tree diagram or 'forest plot' is used. This graph shows the information from each study, including a representation of each study's statistical weight relative to its confidence intervals and the standard error of the mean. For example, in a forest plot of a meta-analysis of 10 studies, the horizontal lines indicate each study's confidence interval.

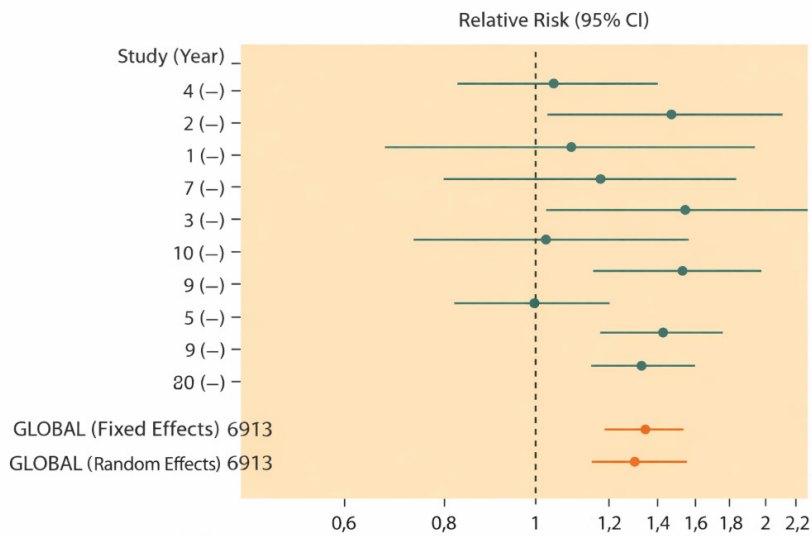

Figure 6.4. Graphical representation of an MA under the tree diagram structure

Interpretation of results: finally, a Systematic Review (SR) culminates with the interpretation of its findings. This involves a discussion of the limitations of the review, including possible biases in the original studies and those that may have affected the SR. It is also crucial to analyze the

consistency and applicability of the results and to make recommendations for future research related to the topic of interest.

Conclusions: Systematic Reviews (SRs) are essential for consolidating existing scientific information, strengthening the validity of individual study conclusions, and identifying areas where further research is needed. Conducting an SR must follow a rigorous methodology and quality control to avoid bias in the conclusions. Although SRs are very important in Evidence-Based Clinical Practice (EBCP), the final decision on a patient's treatment rests with the clinician. SRs are an additional tool that should be used judiciously in decision-making. To facilitate clinicians' critical evaluation and the incorporation of their results into optimal clinical decision-making, several methodological steps have been proposed.