31. Systematic Review vs. Meta-analysis

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1. What is the difference between a systematic review and a meta-analysis?

Systematic reviews and meta-analyses are distinct types of secondary research, that is, studies that compile the results of multiple independent primary studies in a single work. Primary studies are original investigations designed and conducted to answer a specific research question.

A **systematic review** aims to identify, retrieve, screen, appraise, and synthesize relevant primary studies to address a predefined research question. Systematic reviews differ from narrative literature reviews in that they employ transparent, methodologically sound, and unbiased procedures that ensure reproducibility. A systematic review may or may not be followed by a meta-analysis, which consists of a quantitative synthesis of data extracted from the primary studies.

A **meta-analysis** is a set of statistical methods that enables the combination (quantitative synthesis) of the results of two or more independent studies into a single estimate, often referred to as an "analysis of analyses." The primary studies included in a meta-analysis may or may not originate from a systematic review. Although the two approaches can be made independently, coupling a systematic review with a meta-analysis is ideal when the objective is to combine quantitative results from multiple primary studies available in the literature.

2. How to conduct high-quality systematic reviews and meta-analyses?

Several guides and manuals provide detailed recommendations for conducting high-quality systematic reviews and meta-analyses. In the clinical field, we highlight the guidelines of the Cochrane Collaboration and the Joanna Briggs Institute. For preclinical research, particularly studies involving experimental animals, we recommend the manuals developed by the **CAMARADES** and **SYRCLE** initiatives. CAMARADES manuals are available in Portuguese on the CAMARADES Brazil website (https://camaradesbrasil.bio.br/). Reporting of systematic reviews and meta-analyses should follow the **PRISMA** (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines.

We suggest the following steps when developing a systematic review and meta-analysis in your research field:

2.1. Select a topic of interest and verify whether there are ongoing systematic reviews addressing it. If such reviews exist, consider choosing a different topic or collaborating with the existing review group. If not, proceed with your plan.

2.2. Develop a protocol detailing the procedures for each stage of the review, including:

- Formulation of the review question
- Literature search strategy
- Study selection
- Data extraction
- Assessment of the validity (risk of bias) of included studies
- Analytical plan (qualitative synthesis and/or meta-analysis)
- Dissemination of results

2.3. Register, deposit, or publish the protocol in a public repository (e.g., PROSPERO) or in an academic journal.

2.4. Conduct the review according to the procedures specified in the protocol.

2.5. Prepare the manuscript and submit the results of the review for publication in a scientific journal.

3. Meta-analysis using data from a systematic literature review

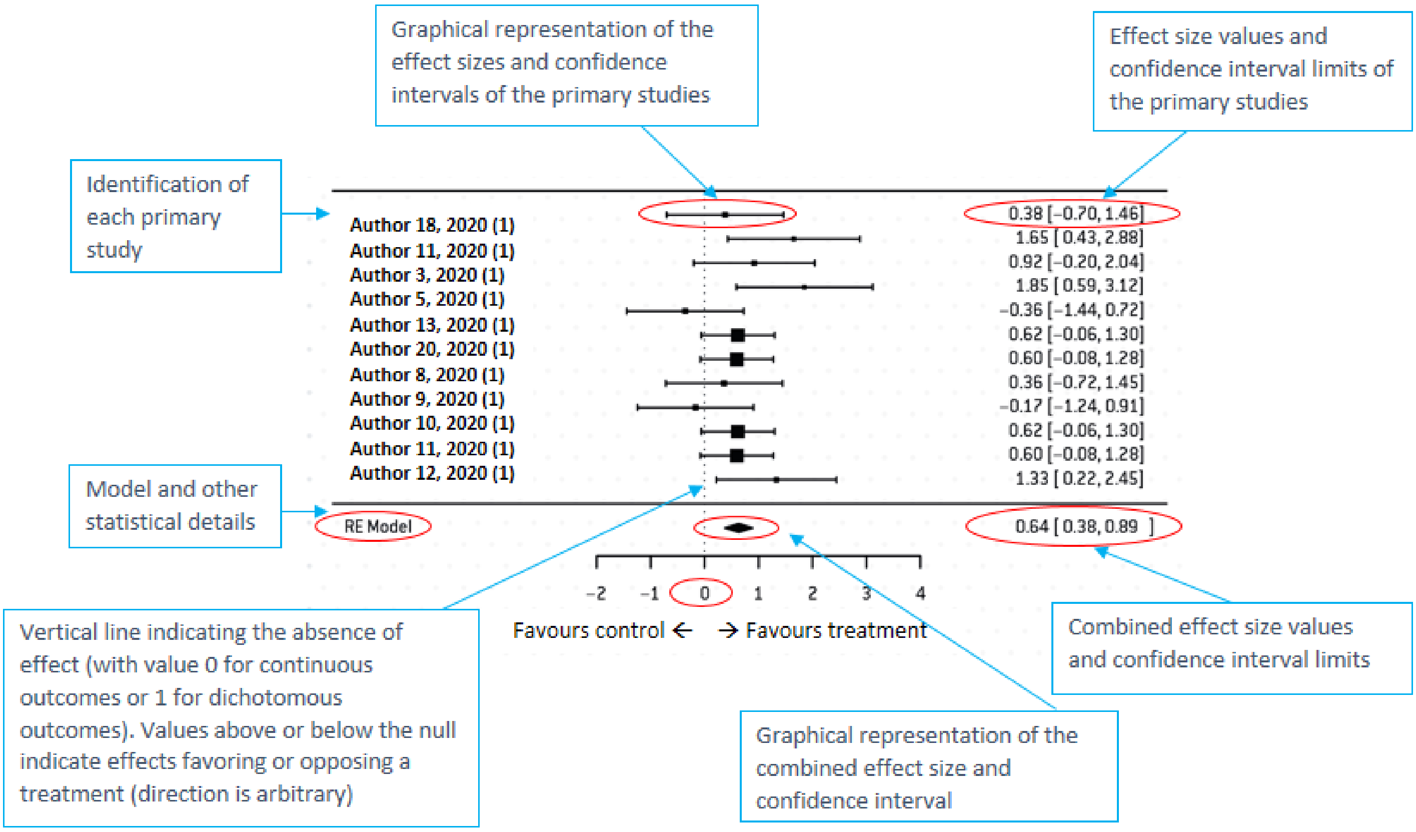
In most meta-analyses, the synthesized quantitative output consists of **effect size estimates,** statistics that describe the magnitude and direction of the association between two variables (e.g., intervention vs. control, incidence, prevalence). Examples include:

Estimate	What it represents
Standardized mean differences (Cohen's *d*, Hedges' *g*, Cohen's d_m, etc.)	Magnitude and direction of the difference between two groups, such as control vs. treated, assuming similar standard deviations (Cohen's *d*), different sample sizes (Hedges' *g*), or paired observations (e.g., before vs. after treatment, Cohen's d_m).
Probability ratios (relative risk, risk ratio, odds ratio)	Magnitude of the risk of an event occurring or not occurring, expressed as the ratio of probabilities between experimental groups (independent or paired).
Correlation coefficient (Pearson's *r*)	Magnitude of the correlation between two outcomes recorded within the same group (e.g., pre- and post-treatment).

In a meta-analysis, the effect sizes from individual primary studies are synthesized into a single summary estimate known as the **combined effect size**, which is accompanied by measures of uncertainty such as confidence and prediction intervals. The combined effect size is calculated as a weighted average of the effect sizes from the primary studies. Each study's weight is determined by its variance and sample size: the smaller the variance and the larger the sample size, the greater its weight. Different statistical models, most commonly **fixed-effect** and **random-effects** models, apply weights differently based on their assumptions regarding the absence (fixed-effect) or presence (random-effects) of heterogeneity among studies.

4. Forest plots for presenting meta-analysis results

Meta-analysis results are commonly presented using **forest plots**, which visually display the effect sizes of individual studies and the combined effect size, together with their measures of uncertainty, in a single figure. Traditionally, although not obligatorily, the combined effect size is represented by a **diamond**, whose left and right tips correspond to the confidence interval limits. If the diamond touches or crosses the **line of no effect**, the null value is a plausible estimate for the combined effect size (no significant effect). Conversely, when the diamond lies entirely on one side of the null-effect line, the effect is interpreted as statistically significant. The direction in which the diamond departs from the null indicates whether the effect favors the treatment of interest (e.g., treatment vs. control).



Example of a hypothetical forest plot.

5. What are the applications of systematic reviews and meta-analyses?

In the medical sciences, these methods are highly valued for evidence-based decision-making. In basic research, including Pharmacology, systematic reviews and meta-analyses can guide the development of new projects by identifying which experimental designs, protocols, or procedures have been most effective in previous studies, thereby increasing the likelihood of success in future research.

Regardless of the field of application, the reliability of conclusions drawn from systematic reviews and meta-analyses depends on the methodological rigor of the review and on the quality of the primary studies included.

6. Conclusions

Systematic reviews and meta-analyses are valuable tools for reviewing, describing, synthesizing, and analyzing accumulated knowledge in a research field. They also help identify and explain heterogeneity and inconsistencies among studies addressing the same topic.

7. References

Borenstein M., Hedges L.V., Higgins J.P. and Rothstein H.R. *Introduction to Meta-Analysis*. John Wiley & Sons, 2021.

Higgins J.P.T., Thomas J., Chandler J., Cumpston M., Li T., Page M.J. at al. (eds.). *Cochrane Handbook for Systematic Reviews of Interventions*, version 6.3 (updated February 2022). Cochrane, 2022. Available from www.training.cochrane.org/handbook.