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REVIEW

Systematic review and meta-analysis

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Abstract In this review the usual methods applied in systematic reviews and meta-analyses are outlined. The ideal hypothesis for a systematic review should be generated by information not used later in meta-analyses. The selection of studies involves searching in web repertories, and more than one should be consulted. A manual search in the references of articles, editorials, reviews, etc. is mandatory. The selection of studies should be made by two investigators on an independent basis. Data collection on quality of the selected reports is needed, applying validated scales and including specific questions on the main biases which could have a negative impact upon the research question. Such collection also should be carried out by two researchers on an independent basis. The most common procedures for combining studies with binary outcomes are described (inverse of variance, Mantel-Haenszel, and Peto), illustrating how they can be done using Stata commands. Assessment of heterogeneity and publication bias is also illustrated with the same program.

PALABRAS CLAVE
Revisión sistemática;
Metaanálisis;
Heterogeneidad;
Sesgo de publicación

Revisión sistemática y metaanálisis

Resumen En esta revisión se detallan los métodos habituales que se aplican en una revisión sistemática con metaanálisis. La hipótesis ideal para una revisión sistemática es la generada por el material científico que no formará parte del metaanálisis. La selección de los estudios supone la búsqueda en más de un repertorio en la web. Es obligatoria una búsqueda manual en la bibliografía de artículos, editoriales, revisiones, etc. La selección de los estudios debería hacerse por 2 investigadores independientes. Hay que reunir información sobre la calidad de

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los estudios, aplicando escalas validadas en las que deben constar preguntas específicas sobre los sesgos que pueden amenazar a la pregunta de investigación, por 2 investigadores independientes. Se describen los métodos más comunes para combinar estudios con efectos binarios (inverso de la varianza, Mantel-Haesnzel y Peto), y se muestra cómo hacerlo con comandos de Stata. La valoración de la heterogeneidad y del sesgo de publicación se ilustran con el mismo programa.

The term ''meta-analysis'' was created before the concept of systematic review. It was coined by Glass in 1976[1] to define a pool of statistical procedures to combine the results of several studies addressing the same research question. The Cochrane Collaboration defines ''systematic review'' as the synthesis of the results of several primary studies using techniques which decrease the risk of both bias and random error.[2] The unit of research is not the individual, but the research study. Currently, meta-analysis is restricted to the data analysis of a systematic review.

In theory, a systematic review can be applied to any research question, either on etiology (e.g., the association between body mass index and clinical outcome for patients with acute respiratory distress syndrome[3]), diagnosis (e.g., the assessment of diagnostic accuracy of urinary TIMP-2·IGFBP7 for acute kidney injury in adults[4]), prognosis (e.g., high-flow nasal cannula oxygen therapy in adults with acute hypoxemic respiratory failure[5]) or any intervention, either preventive (e.g., prone position ventilation in patients with acute respiratory distress[6]) or therapeutic (e.g., the use of fibrinolytics in acute myocardial infarction – AMI-7). The general objectives of a systematic review can be:

1. The assessment of consistency (or its absence, that is, presence of heterogeneity) across the primary studies; for instance, the treatment with fibrinolytics in AMI was highly heterogeneous across 33 studies, being due mainly to the delay in using the drug.[7]
2. To obtain an overall estimator of an association. In the meta-analysis of fibrinolytics, the pooled odds ratio – OR – was 0.83, highly significant ($p < 0.001$).[7]
3. To identify the subgroups where an exposure (a test, treatment, etc.) shows a higher or lower strength of association. Fibrinolytics increase AMI mortality in the short term (first 48 h), although it is widely outweighed in the long term.[7] Meta-analysis failed in identifying any subgroup at an increased risk of death in the short term.[8]
4. The assessment of quality of the primary studies to offer a guide for future studies on the subject.

Stages

The outline of a systematic review is as follows[9]:

1. A research question based on a hypothesis.
2. Selection of the study population (primary studies):
   (a) Sources of data.
   (b) Search criteria and inclusion criteria.
3. Data collection: assessment of the validity of primary studies and extraction of relevant data.
4. Meta-analysis:
   (a) Statistical methods to combine data.
   (b) Assessment of heterogeneity in the pooled estimates.
   (c) Ascertainment of publication bias.

Origin of the hypothesis

It is important to remember that a basic principle of research is that a hypothesis cannot be proved using the sample which suggested it. This is very common in systematic reviews, where investigators read some studies, note that they are not consistent (no firm recommendation can be derived from them) and decide to carry out a systematic review, in which the studies which gave the idea are also included in the meta-analysis. This procedure caused in the past rejection of meta-analysis as a method of research by prestigious scientists.[10]

The ideal situation is that the hypothesis would be originated in a sort different of research. For instance, in the association between garlic intake and risk of cancer the idea was suggested by experimental studies on rats fed with a diet enriched in garlic[11]: this launched a search of epidemiologic studies in humans to assess the relationship.

Selection of the study population

Search of studies

General strategies

The reference population in a systematic review are all the researches carried out on a subject in the world. There are several strategies:

1. To search all the available information, either published or not. To get unpublished studies is not easy. As an approach, a researcher can consult theses, grants and projects funded by agencies (governmental and private), presentations at scientific meetings, interviews to specialists on the topic, etc. This strategy tries to minimize publication bias.

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