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A comprehensive review on systematic and Meta-analysis methods

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Abstract

Systematic reviews and meta-analyses are being increasingly used to summarize medical literature and identify areas in which research is needed. Systematic reviews limit bias with the use of a reproducible scientific process to search the literature and evaluate the quality of the individual studies. If possible the results are statistically combined into a meta-analysis in which the data are weighted and pooled to produce an estimate of effect. This article aims to provide with an overview of systematic review and meta-analysis methodology.

Key-Words: Systematic, Meta analysis, Methodology

Introduction

Meta-analysis is a statistical procedure that integrates the results of several independent studies considered to be “combinable.” Well conducted meta-analyses allow a more objective appraisal of the evidence than traditional narrative reviews, provide a more precise estimate of a treatment effect, and may explain heterogeneity between the results of individual studies. Meta-analysis combines the results of several studies that address a set of related research hypotheses. In its simplest form, this is normally by identification of a common measure of effect size, for which a weighted average might be the output of a meta-analysis. Here the weighting might be related to sample sizes within the individual studies. More generally there are other differences between the studies that need to be allowed for, but the general aim of a meta-analysis is to more powerfully estimate the true "effect size" as opposed to a smaller "effect size" derived in a single study under a given single set of assumptions and conditions. Meta-analyses are often, but not always, important components of a systematic review procedure. Here it is convenient to follow the terminology used by the Cochrane Collaboration,[1] and use "meta-analysis" to refer to statistical methods of combining evidence, leaving other aspects of 'research synthesis' or 'evidence synthesis', such as combining information from qualitative studies, for the more general context of systematic reviews.[1]

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The first meta-analysis was performed by Karl Pearson in 1904, in an attempt to overcome the problem of reduced statistical power in studies with small sample sizes; analyzing the results from a group of studies can allow more accurate data analysis. However, the first meta-analysis of all conceptually identical experiments concerning a particular research issue, and conducted by independent researchers, has been identified as the 1940 book-length publication *Extra-sensory perception after sixty years*, authored by Duke University psychologists J. G. Pratt, J. B. Rhine, and associates.[2] This encompassed a review of 145 reports on ESP experiments published from 1882 to 1939, and included an estimate of the influence of unpublished papers on the overall effect (the *file-drawer problem*). Although meta-analysis is widely used in epidemiology and evidence-based medicine today, a meta-analysis of a medical treatment was not published until 1955. In the 1970s, more sophisticated analytical techniques were introduced in educational research, starting with the work of Gene V. Glass, Frank L. Schmidt and John E. Hunter.

Gene V Glass was the first modern statistician to formalize the use of meta-analysis, and is widely recognized as the modern founder of the method. The online Oxford English Dictionary lists the first usage of the term in the statistical sense as 1976 by Glass.[3] The statistical theory surrounding meta-analysis was greatly advanced by the work of Nambury S. Raju, Larry V. Hedges, Harris Cooper, Ingram Olkin, John E. Hunter,

Jacob Cohen, Thomas C. Chalmers, Robert Rosenthal and Frank L. Schmidt.

Advantages of meta-analysis[3-8]

Advantages of meta-analysis (e.g. over classical literature reviews, simple overall means of effect sizes etc.) include:

- Shows if the results are more varied than what is expected from the sample diversity
- Derivation and statistical testing of overall factors / effect size parameters in related studies
- Generalization to the population of studies
- Ability to control for between-study variation
- Including moderators to explain variation
- Higher statistical power to detect an effect than in 'n=1 sized study sample'
- Deal with information overload: the high number of articles published each year.
- It combines several studies and will therefore be less influenced by local findings than single studies will be.
- Makes it possible to show if a publication bias exists.

Steps in a meta-analysis

1. Formulation of the problem
2. Search of literature
3. Selection of studies ('incorporation criteria')
   - Based on quality criteria, e.g. the requirement of randomization and blinding in a clinical trial
   - Selection of specific studies on a well-specified subject, e.g. the treatment of breast cancer.
   - Decide whether unpublished studies are included to avoid publication bias (file drawer problem)
4. Decide which dependent variables or summary measures are allowed. For instance:
   - Differences (discrete data)
   - Means (continuous data)
   - Hedges' *g* is a popular summary measure for continuous data that is standardized in order to eliminate scale differences, but it incorporates an index of variation between groups:

$$\delta = \frac{\mu_t - \mu_c}{\sigma};$$

in which μ_t is the treatment mean, μ_c is the control mean, σ^2 the pooled variance.

5. Model selection (see next paragraph)

For reporting guidelines, see QUOROM statement

Meta-regression models

Generally, three types of models can be distinguished in the literature on meta-analysis: simple regression, fixed effect meta-regression and random effects meta-regression.

Simple regression

The model can be specified as

$$y_j = \beta_0 + \beta_1 x_{1j} + \beta_2 x_{2j} + \cdots + \varepsilon$$

Where y_j is the effect size in study *j* and β_0 (intercept) the estimated overall effect size. The variables

$$x_i (i = 1 \ldots k)$$

specify different characteristics of the study, ε specifies the between study variation. Note that this model does not allow specification of within study variation.

Fixed-effect meta-regression

Fixed-effect meta-regression assumes that the true effect size θ is normally distributed with

$$\mathcal{N}(\theta, \sigma_\theta)$$

where σ^2_θ is the within study variance of the effect size. A fixed effect meta-regression model thus allows for within study variability, but no between study variability because all studies have the identical expected fixed effect size θ, i.e. ε = 0. ***Note that for the "fixed-effect" no plural is used (in contrast to "random-effects") as only ONE true effect across all datasets is assumed.

$$y_j = \beta_0 + \beta_1 x_{1j} + \beta_2 x_{2j} + \cdots + \eta_j$$

Here $\sigma^2_{\eta_j}$ is the variance of the effect size in study *j*. Fixed effect meta-regression ignores between study variation. As a result, parameter estimates are biased if between study variation can not be ignored. Furthermore, generalizations to the population are not possible.

Random effects meta-regression

Random effects meta-regression rests on the assumption that θ in

$$\mathcal{N}(\theta, \sigma_i)$$

is a random variable following a (hyper-)distribution

$$\mathcal{N}(\theta, \sigma_\theta).$$

A random effects meta-regression is called a mixed effects model when moderators are added to the model.

$$y_j = \beta_0 + \beta_1 x_{1j} + \beta_2 x_{2j} + \cdots + \eta + \varepsilon_j$$

Here $\sigma^2_{\varepsilon_j}$ is the variance of the effect size in study *j*.

Between study variance σ^2_η is estimated using common estimation procedures for random effects models (restricted maximum likelihood (REML) estimators).

Observational study of evidence[7-9]

Meta-analysis should be viewed as an observational study of the evidence. The steps involved are similar to any other research undertaking: formulation of the problem to be addressed, collection and analysis of the data, and reporting of the results. Researchers should write in advance a detailed research protocol that clearly states the objectives, the hypotheses to be tested, the subgroups of interest, and the proposed methods and criteria for identifying and selecting relevant studies and extracting and analysing information.

As with criteria for including and excluding patients in clinical studies, eligibility criteria have to be defined for the data to be included. Criteria relate to the quality of trials and to the combinability of treatments, patients, outcomes, and lengths of follow up. Quality and design features of a study can influence the results. Ideally, researchers should consider including only controlled trials with proper randomization of patients that report on all initially included patients according to the intention to treat principle and with an objective, preferably blinded, outcome assessment. Assessing the quality of a study can be a subjective process, however, especially since the information reported is often inadequate for this purpose. It is therefore preferable to define only basic inclusion criteria and to perform a thorough sensitivity analysis.

The strategy for identifying the relevant studies should be clearly delineated. In particular, it has to be decided whether the search will be extended to include unpublished studies, as their results may systematically differ from published trials. As will be discussed in later articles, a meta-analysis that is restricted to published evidence may produce distorted results owing to such publication bias. For locating published studies, electronic databases are useful, but, used alone, they may miss a substantial proportion of relevant studies. In an attempt to identify all published controlled trials, the Cochrane Collaboration has embarked on an extensive manual search of medical journals published in English and many other languages. The Cochrane Controlled Trials Registeris probably the best single electronic source of trials; however, citation indices and the bibliographies of review articles, monographs, and the located studies should also be scrutinised.

Standardised outcome measure

Individual results have to be expressed in a standardised format to allow for comparison between studies. If the end point is continuous—for example, blood pressure—the mean difference between the treatment and control groups is used. The size of a difference, however, is influenced by the underlying population value. An antihypertensive drug, for example, is likely to have a greater absolute effect on blood pressure in overtly hypertensive patients than in borderline hypertensive patients. Differences are therefore often presented in units of standard deviation. If the end point is binary—for example, disease versus no disease, or dead versus alive) then odds ratios or relative risks are often calculated (box). The odds ratio has convenient mathematical properties, which allow for ease in combining data and testing the overall effect for significance. Absolute measures, such as the absolute risk reduction or the number of patients needed to be treated to prevent one event, are more helpful when applying results in clinical practice

Applications in modern science

Modern statistical meta-analysis does more than just combine the effect sizes of a set of studies. It can test if the outcomes of studies show more variation than the variation that is expected because of sampling different research participants. If that is the case, study characteristics such as measurement instrument used, population sampled, or aspects of the studies' design are coded. These characteristics are then used as predictor variables to analyze the excess variation in the effect sizes. Some methodological weaknesses in studies can be corrected statistically. For example, it is possible to correct effect sizes or correlations for the downward bias due to measurement error or restriction on score ranges.

Meta-analysis can be done with single-subject design as well as group research designs. This is important because much of the research on low incidents populations has been done with single-subject research designs. Considerable dispute exists for the most appropriate meta-analytic technique for single subject research.9

Meta-analysis leads to a shift of emphasis from single studies to multiple studies. It emphasizes the practical importance of the effect size instead of the statistical significance of individual studies. This shift in thinking has been termed "meta-analytic thinking". The results of a meta-analysis are often shown in a forest plot.

Results from studies are combined using different approaches. One approach frequently used in meta-analysis in health care research is termed 'inverse variance method'. The average effect size across all studies is computed as a weighted mean, whereby the weights are equal to the inverse variance of each study’s effect estimator. Larger studies and studies with less random variation are given greater weight than smaller studies. Other common approaches

include the Mantel–Haenszel method and the Peto method.

A recent approach to studying the influence that weighting schemes can have on results has been proposed through the construct of *gravity*, which is a special case of combinatorial meta-analysis.

Signed differential mapping is a statistical technique for meta-analyzing studies on differences in brain activity or structure which used neuroimaging techniques such as fMRI, VBM or PET.

Comparison of meta-analysis to the scientific method[9-11]

Francis Bacon described a method of procedure for advancing the physical sciences.

Aphorism 106: In forming our axioms from induction, we must examine and try whether the axiom we derive be only fitted and calculated for the particular instances from which it is deduced, or whether it be more extensive and general. If it be the latter, we must observe, whether it confirms its own extent and generality by giving surety, as it were, in pointing out new particulars, so that we may neither stop at actual discoveries, nor with a careless grasp catch at shadows and abstract forms, instead of substances of a determinate nature: and as soon as we act thus, well authorized hope may with reason, be said to beam upon us.

George Boole gave a similar description .

The study of every department of physical science begins with observation; it advances by the collation of facts to a presumptive acquaintance with their connecting law, the validity of such presumption it tests by new experiments so devised as to augment, if the presumption be well founded, its probability indefinitely; and finally, the law of the phenomenon having been with sufficient confidence determined, the investigation of causes, conducted by the due mixture of hypothesis and deduction, crowns the inquiry.

In both descriptions there are three steps: first assemble data, second formulate an explanatory physical law, and third test the proposed physical law in future experiments. In a meta analysis the first two steps are carried out, but the third step is modified. Meta-analysis being retrospective has no data gathered after the formulation of the physical law and so confirms the physical law using data that were known at the time the physical law was formulated. This requires a change from the usual notion of probability: Probability is expectation founded upon partial knowledge. A perfect acquaintance with all the circumstances affecting the occurrence of an event would change expectation into certainty, and leave neither room nor demand for a theory of probabilities. Statistical significance in a hypothesis test is the probability rejecting the null hypothesis when it is true. In the scientific method, statistical significance is the probability of a future event. In a meta-analysis, statistical significance is the probability of a past event.

In a meta-analysis the analyst has "perfect acquaintance with all the circumstances affecting the occurrence" of any event defined by the data at the time the hypotheses are specified. So there is no uncertainty and the probabilities of such events, using Boole's notion of probability, would be zero or one. The procedure in meta-analysis is to simulate necessary incompleteness of knowledge by calculating the power and statistical significance as if none of the data were known to the analyst at the time the hypotheses were specified. A meta-analysis hypothesis test is, within the context of the scientific method of Bacon and Boole, a simulated hypothesis test.

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